FORMULATION AND EVALUATION OF IMMEDIATE RELEASE BILAYER TABLETS OF AMLODIPINE BESYLATE AND LOSARTAN POTASSIUM

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

Register Number: 26111011

UNDER THE GUIDANCE

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Approved by Pharmacy Council of India, New Delhi, and
All India Council for Technical Education. New Delhi.

CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND EVALUATION OF IMMEDIATE RELEASE BILAYER TABLETS OF AMLODIPINE BESYLATE AND LOSARTAN POTASSIUM"** submitted to **THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY, CHENNAI-32** for the award of the degree **Master of pharmacy in Pharmaceutics** is a bonafide research work done by **Register No: 26111011** under my Guidance in the Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Chennai-600 097 during the academic year 2012-2013.

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ACKNOWLEDGEMENT

It is a great time for me to acknowledge those without whom, this work would not have been fruitful.

It gives me an immense pleasure in expressing my deep sense of gratitude to my respected guide **Mrs. Rama, M.Pharm., (Ph.D) M. Pharm., Assistant professor, C.L.Baid Metha college of pharmacy,Chennai-97** for her remarkable guidance, constant encouragement and every scientific and personal concern throughout the course of investigation and successful completion of this work.

I would like to express my immense gratitude to my Industrial guide **Mr. V. Prabhakaran,Manager, Madras Pharmaceuticals limited, Chennai** for providing the great opportunity to carry out the project with his valuable guidance and support in each and every aspect of the project.

It is great pleasure and honour for me to owe gratitude to **Dr. Grace Rathnam M.Pharm, Ph.D**. principal for all her support and for giving a valuable guidance and scientific support to carry out this work.

I would like to thank Madras Pharmaceuticals limited, for giving me an opportunity to perform my project work in their organization which helped me to mould my project work into a successful one.

I feel proud to express my hearty gratitude and appreciation to all my Teaching and Non-teaching Staff members of **C.L.Baid Metha College of Pharmacy,Chennai-97** who encouraged to complete this work.

I feel proud to express my hearty gratitude to all my classmates. Also I want to thank all of those, whom I may not be able to name individually, for helping me directly or indirectly.

Last but not the least I wish to express my deepest sense to respect and love to my parents for their constant support and encouragement throughout.

(Reg.No: 26111011)

Dedicated To

my

Beloved Family

&

My friends

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ABBREVIATIONS

API	Active pharmaceutical Ingredient
HPMC	Hydroxy propyl methyl cellulose
IPA	Iso Propyl Alcohol
HPLC	High performance liquid chromatography
FTIR	Fourier transformer infrared spectroscopy
RH	Relative Humidity
USP	United States Pharmacopoeia
IP	Indian Pharmacopoeia
CI	Compressibility Index
HR	Hausner Ratio
WHO	World Health Organisation
IR	Immediate Release
DDS	Drug Delivery System
GI	Gastro Intestinal Tract
CCB	Calcium Channel Blocker
ACE	Angiotensin Converting Enzyme
ARB	Angiotensin Receptor Blocker
AR	Analytical Reagent
RPM	Rotation Per Minute
FBD	Fluidized Bed Dryer
ICH	International Conference on Harmonisation

NOMENCLATURE

%	Percentage
µg/ml	Microgram/millilitre
Conc	Concentration
gm/cc	Gram/cubic centimetre
Hr	Hour
Kg/cm2	Kilogram/square centimetre
Min	Minute
Mm	Millimetre
Sec	Seconds
Hr	Hour
SD	Standard Deviation

Introduction

1. INTRODUCTION

Oral drug delivery system is considered to be one of the most convenient and commonly employed drug delivery system as it possesses some specific advantageous characteristics, such as ease of administration, least aseptic constraints and flexibility in the design of the dosage form. Another revolution towards the oral drug delivery is the modified release dosage forms which have huge advantages over immediate release formulations of the same drug. There are different methods for the designing of this modified dosage form, some of them are film coated pellets, tablets, capsules or more sophisticated and complicated delivery systems such as osmotically driven systems, systems controlled by ion exchange mechanism, systems using three dimensional printing technology and systems using electrostatic deposition technology. The modified release products are usually designed to provide slow and continuous delivery of drug over the entire dosing interval and improve patient compliance and convenience[1,2,3]. Recently, the most common widely used controlled delivery system is the matrix type where the drug is uniformly entrapped in to the polymer[4,5]. In formulation of oral controlled release formulation, hydrophilic polymers are most frequently used as polymeric retardant materials due to their ease of manufacturing, relatively low cost, favorable *in vivo* performance and versatility in controlling the release of drug with wide range of physicochemical properties[6-11].The release of highly water soluble drug inherently follows near first-order diffusion with an initially high release rate. The enhanced release rate observed at the beginning within a short period of time and it is known as burst effect, sometimes it is undesirable as it can have some negative therapeutic impact (i.e. toxicity due to increase of the concentration of the delivered substance beyond maximum therapeutic concentration).After this burst effect, hydration and consequent swelling and/or erosion of retard polymer occurs. These

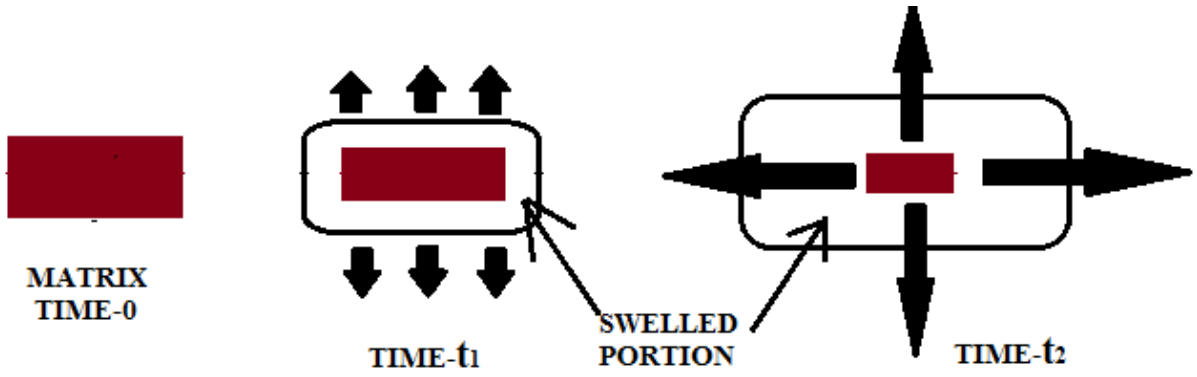
phenomena control the release process but sometimes this result in a progressively slow release rate as due the increasing of the diffusion path-length, as a result of which ultimately a saturation effect is attained[6-11]. A number of factors that are used to overcome this undesirable behavior and release pattern of drug from polymeric matrix include physicochemical properties of drug (solubility, viscosity, etc.),content of drugs and polymers in matrices,drug/polymer weight ratio, route of administration,and manufacturing process[12-19].

The another new drug delivery concept is the control release of drug form the dosage form where the drug is released from the dosage form in a constant manner in respect to time but without depending upon the initial concentration of the drug and hence the release of drug from this type of dosage form follows zero order release kinetics.This drug delivery system has been widely used as drug delivery system for the drugs having low therapeutic index to reduce the dose dumping. To alter the kinetics of drug release from inherent non-linear behavior to linear include the use of geometry factors (solid units having spherical, cylindrical, conical, biconcave, biconvex, donut shapes, hemisphere with cavity, core in cup, circular sectioned cylinder, rings, oval bi-dose divisible tablets etc.), films, erosion/dissolution controlled and swelling controlled mechanisms, non-uniform drug loading and matrix-membrane combination[20-33]. Among all the above techniques, multi-layered matrix tablet pay more attention as drug delivery devices to the research scientist.

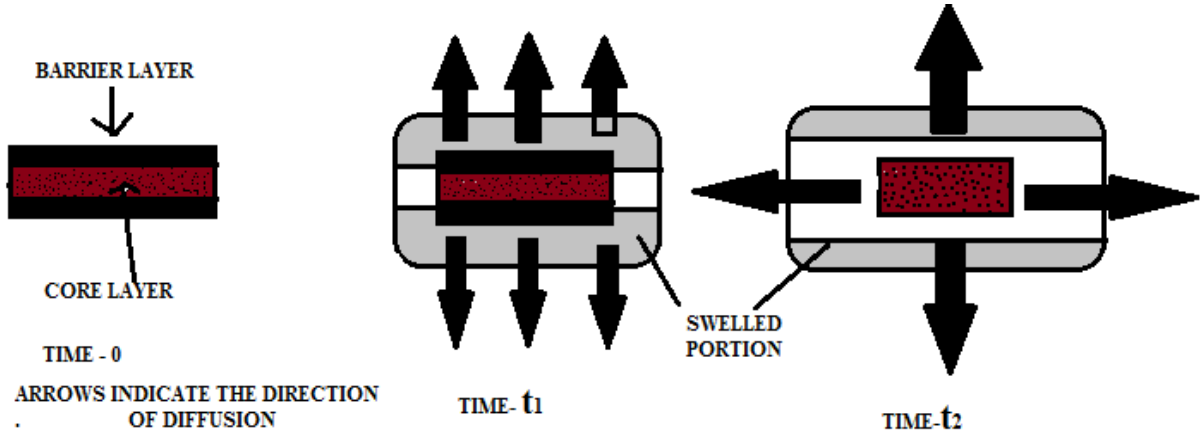
Multi-layered matrix tablet comprises a matrix core containing the active solute(s) and one, or more barriers (modulating layers) incorporated during the tabletting process. The function of the modulating layers is to delay the interaction of active solute with dissolution medium by limiting the surface available for the solute release and at the same time controlling solvent penetration

rate through the matrix[34,35,36]. In this design, the coat layers prevent the water penetration and thus protect the core. This ultimately reduced the hydration rate and controlled area for solute release at the core. Thus burst effect can be minimized and the release can be maintained at a relatively constant level during the barrier layers' swelling and erosion process. After this phase, during the subsequent portion of the dissolution process, these swollen barriers are erosion dominated and the surface available for drug release slowly increases. In this way the decrease of delivery rate due to the increase of diffusion path-length (saturation effect) is counter balanced by the simultaneous increase of the area available for drug release[35].

PLAIN MATRIX TABLET



MULTILAYERD TABLETS (SWELLABLE BARRIERS)



MULTILAYERD TABLETS (ERODIBLE BARRIERS)

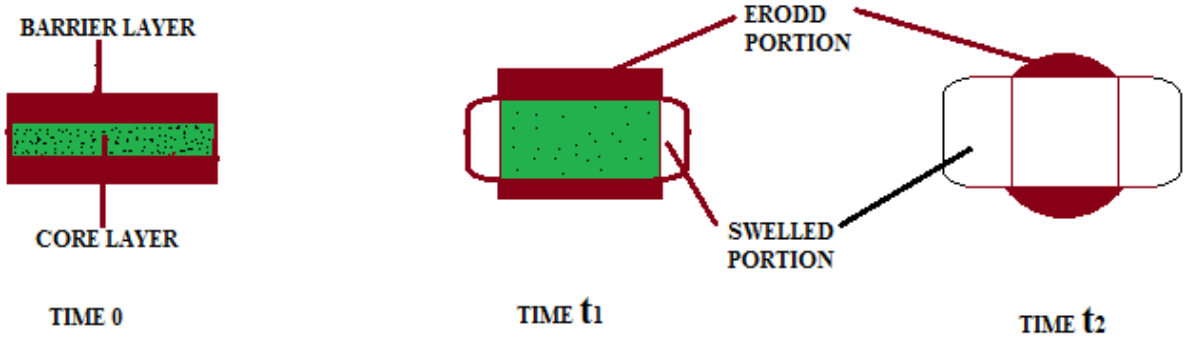


Figure 1: Effect of the application of polymeric layers (barriers) on the release of drug from a matrix core.

A linear release profile is achieved by combining a time-dependent control of the hydration rate of the device with the reduction of tablet surface exposed to the dissolution medium. It is also possible to obtain various dissolution patterns such as multi modal, pulsatile or delayed delivery, extended release (characterized by reasonably constant rate) for different drugs by varying the formulations of layers. The major criterion for all of this application is the multi-layered system should swell gel and finally erode completely, leaving negligible residue in the gastro-intestinal tract[36].The system overcomes the major disadvantage of non-linear release associated with most diffusion controlled matrix devices. Beside the above, this system also has the advantage of being compatible with conventional manufacturing methods. From the word 'Bilayer Tablet' indicates that it is a solid oral dosage form, usually round, spherical, oval or biconcave in shape and consist of one or more than one medicaments designed in a two layers system which can be suitable for combination therapy and biphasic release therapy. In case of combination therapy the two layers of this tablet is consist of two different medicaments and in case of bi-phasic release bilayer tablet both the layers content same drugs but the drug from one layer is immediately release and the drug release from the second layer is released for an extended period of time to maintained the therapeutic concentration of drug within therapeutic window. For the formulation of layers from different polymers manipulation has been done over more than one rate-controlling polymers and thus allow different types of drug delivery of one or more drugs, i.e. where the drug may be released with a bolus and then as a controlled rate or by targeted drug delivery in the GI tract using pH dependent polymers so in the formulation of bilayer tablets the polymer plays a very important role.

Other than the polymer there are clearly a number of issues which should be taken into

consideration during the production of bilayer tablets. Such as the mechanical strength of bilayer tablets, it has been observed that it do not play an important role as the controlling factor in drug release, but the determination of this property is very essential as it could be beneficial in understanding the adhesion property between various layers and finally providing an improved characterization of the systems.

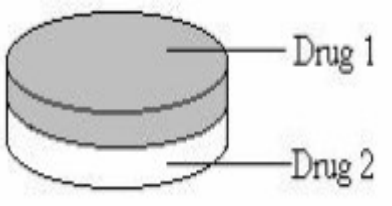


Figure 2: In case of combination therapy the drug 1 and drug 2 are different but in case of sustained release the drug 1 is the loading dose where as the drug 2 is the maintenance dose of a drug

1.1 ADVANTAGES OF BILAYER TABLET

Before explaining the advantages of bilayer tablet, here are the advantages of the tablet dosage form over the dosage form are as follows:

- Tablet is a unit dosage form and they offer the greatest compatibilities of all oral dosage forms for the greatest dose precision and the least content variability.
- The cost is approximately lower than any other oral dosage form.
- These are very compact in nature.
- In general the packaging procedure for tablets are easier and cheaper.
- Swallowing of tablets is very easy.
- They are better suited to large scale production.
- Chemically, mechanically and microbiologically tablets are very stable.

The advantages of the 'bilayer tablet' over the other conventional preparations of oral solid dosage forms include.

- When the two different layers of the tablet content two different drugs, then the tablet can be easily used in combination therapy.
- This formulation can be use to deliver separate two incompatible substance.
- In case of drugs having a low half life, each of the two layers of the tablet respectively content a loading dose and maintenance dose of the same and thus increase the bioavailability of the drug.
- Frequency of the dose administration is reduced which ultimately improve the patient compliance.
- In case of a conventional dosage form due to fluctuation of the dose interval the plasma drug concentration may differ (under medication or over medication), but in this dosage form the plasma drug concentration is always constant, which ultimately provide a more effective action of the drug.
- Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of high availability drug can be reduced by formulation in an extended action form. The safety margin of high potency drugs can be increased and the local and systemic adverse effects can be reduced in sensitive patients.

1.2 LIMITATIONS OF BILAYER TABLET

From the above mentioned advantage of bilayer tablets it is quite clear that in pharmaceutical industry it is a great revolution, but there are certain limitations in the formulation and use of bilayer tablets, such as:

- One of the major challenges in bilayer formulation is lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack and layer separation.
- If the compacted layers are too soft or too hard, they will not bind securely with each other which can lead to compromised mechanical integrity and also the separation of the layers.
- Other challenges during development include establishing the order of layer sequence, layer weight ratio, elastic mismatch of the adjacent layers, first layer tamping force, and cross contamination between layers.
- The adjacent layers of a bilayer tablet are bonded together by mechanical means, so the factors influences the stress state is very important. The mechanical properties of each layer and the tablet, and compression parameters along with specialized techniques and compression condition plays a very important role for the same.
- Administration of sustained release bilayer tablet does not permit the prompt termination of therapy.
- The physician has a less flexibility on adjusting the dose regimens.

1.3 GMP REQUIREMENTS FOR BILAYER TABLET

To produce a quality bi-layer tablet, in a validated and GMP-way, it is very important to follow the following criteria for the selection of bilayer press. These requirements seem obvious but are not so easily accomplish. The press should be capable of

- Preventing capping and separation of the two individual layers that constitute the bi-layer tablet
- Providing sufficient tablet hardness

- Preventing cross-contamination between the two layers
- Producing a clear visual separation between the two layers
- Manufacturing products of high yield
- Accurate and individual weight control of the two layers

1.4 DRUG RELEASE MECHANISM

Normally the drug release from hydrophilic swellable matrices depends on the polymer macromolecular coupling, relaxation and the drug diffusion[11-14] and all of these are responsible on the rate at which water may penetrate into the device. Hydration rate, swelling of the polymer and modification of the polymer matrix are the basics for the multilayered drug delivery design. These factors are very effective at the primary or initial phase of the drug dissolution but with the respect of time as swelling proceeds linearization of the release profile occurs. To achieve this objective, coating of the matrix tablets with an inert impermeable film has been performed. Coating plays a very important role in the drug release from the multilayered preparations and a number of combinations of coating materials are used that is schematically represented by Figure 3. The release rate of the drug from tablets is observed by *in vitro* release rate study. The release rate of the drug is inversely proportional to the extent of coating. The release of the drug is primarily dependant on the swelling of the polymer which is again controlled by reducing the drug release surface by the coating material.

When a tablet is coated partially, it does not swell and retain its initial size and shape and maintain the release retardation continuously through the entire dissolution process[35]. On the other hand, when the tablet is subjected to water immersion the polymer barrier which is inert in nature have a tendency to crack and separated out from the core within hours. This effect is resulted from volume expansion of core upon water immersion due to polymer swelling. The

outer barrier layer does not expand while the core is swelling as a result a stress is generated in the outer barrier layer. When the outer barrier is sellable polymer then the both barrier and core swell simultaneously without any internal stress during the dissolution process. Multilayer compression process can be used for the application of barriers. One notable example of this phenomena is the double layer or three layer tablets in which only one layer contains the active ingredient (active core), while other layers are barrier layers.

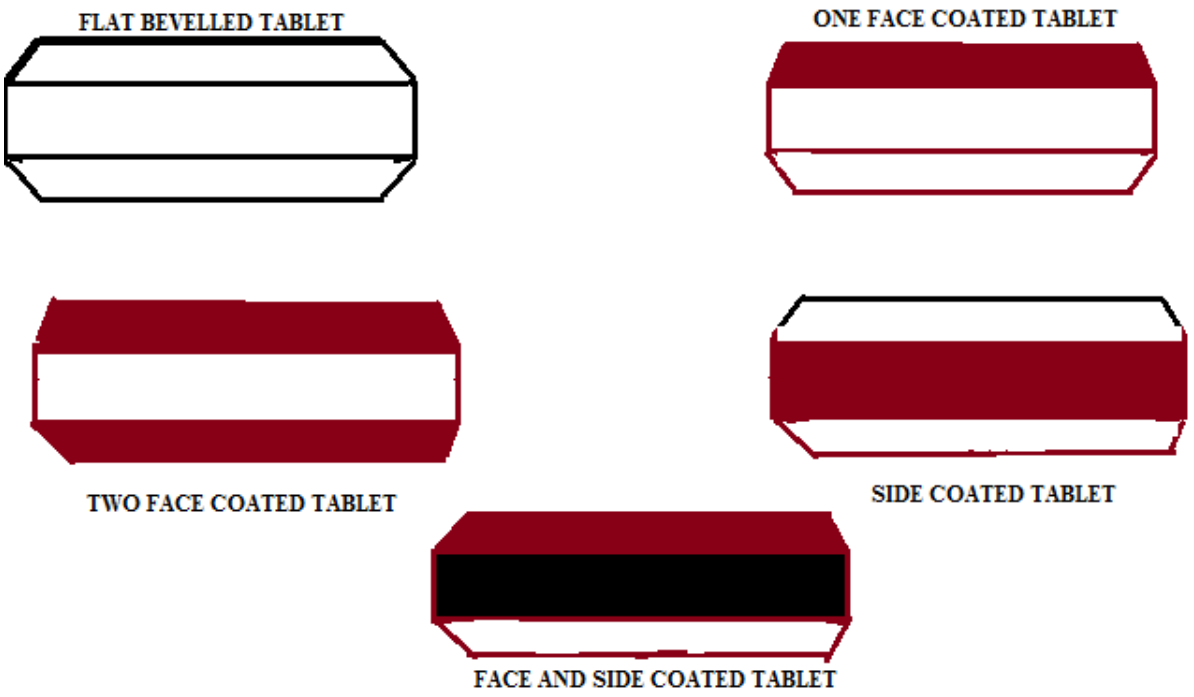


Figure 3: Schematic representation of the matrix tablet (a) and of the four partially coated designs

The multi-layer design allows for the production of different tablet designs by varying the geometry of the device or modulating layers characterized by specific release properties to achieve various dissolution patterns (not limited to a constant release) such as delayed, pulsatile or multi modal delivery profiles. The section below deals with various tablet possibilities based

on this proposed design.

1.5 DIFFERENT STRATEGY OF DRUG RELEASE:

1.5.1 Release of drug follows zero-order release kinetics

Zero order release means where the release of the drug occurred without being dependant on the initial concentration of the drug. This system consists of either a hydrophilic or hydrophobic layer containing the active ingredients or one or two barrier layers. These barrier layers are coated to the faces of the tablet core and the sides of the core remain exposed. The polymers widely used as barrier for sustaining the drug delivery are either hydrophilic or hydrophobic materials. Linear release profiles is usually obtained by applying hydrophilic barrier layers on either the sides of a hydrophobic matrix tablet or by applying a hydrophilic barrier layer on any one side and hydrophobic barrier layer on the other side of the matrix tablet. However, net formulation and variables within the matrix and barrier layers must be controlled to get zero-order release of drug from hydrophilic matrix tablet coated with hydrophobic barrier layers on both the faces[37-40].

1.5.2 Fast/slow release system

In case of designing a dosage form of quick/slow release delivery system an initial rapid release phase is designed by the application of immediate release layer to the conventional layered matrix tablet. Where a drug is initially rapidly released from a dosage form and then followed by a slow release rate. The burst release can suddenly raise the plasma drug concentration which can produce a rapid rise in plasma levels for those drugs that are required to show appearance promptly for the therapeutic effect, followed by an extended release of drug at a constant rate for prolonged period of time. A versatile quick/slow delivery system can be designed one of which is Naproxen quick/slow system developed by Maggi *et al* [41]. This system proved bioequivalence with marketed tablet Naprosyn SR. Thus the quick/slow delivery system

is very essential in certain conditions like where sudden increase of plasma drug concentration is essential for the purpose of getting therapeutic activity immediately as well as to reduce dose frequency and thereby to improve patient compliance[41,42,43].

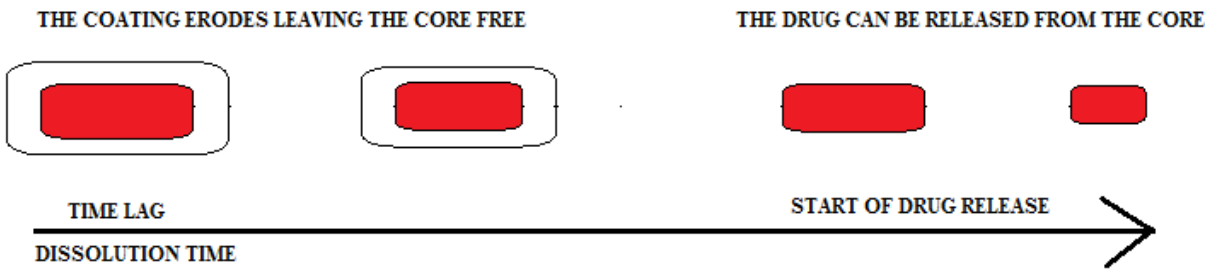
1.5.3 Time-programmed delivery system (press coated tablet)

In certain disease conditions, the rate and behavior of drug release should be controlled with respect to time, as because of maintenance of constant drug plasma concentration is not required for desired therapeutic activity. The drug release behavior should be controlled in respect to time along with the rate of drug release, as because to maintain always a constant drug plasma concentration is not required for the optimal or desired therapeutic activity. Therefore, a drug with optimal concentration should be delivered in target site with respect to time for getting the required activity. In order to reduce the incidence of tolerance and to follow the innate circadian rhythm, the most accepted form of the drug delivery system should be such that the dosage forms capable of release the drug in a pulsatile fashion rather than continuous release[44,45,46,47]. For this purpose, various system like time clock system have been developed using different technique and functional polymers or additives[48,49,50,51].

Press coating technique is one of the novel drug delivery system that not only controls the release of drug but also deliver the drug in gut. No special coating solvent or equipments and manufacturing speed is faster are the main advantages of this techniques. Either conventional or modified release formulation core system is used in this system and the core layer may further coated by different polymers with the help of compression process[52,53]. This system delivers the drug from the core tablet after swelling or eroding of the hydrophilic or hydrophobic barrier of the coating shell to exhibit a pulsatile manner of drug release[54,55,56,57]. The function of this outer shell is to protect the core layer and delay the drug release by prolonging the lag time prior to the start of drug release and control the fluid penetration. This device can be

considered as a reservoir system this phenomenon is not dependent on the composition of the core rather on the shell structure and presence of expandable polymer in the shell. After the fluid penetration the interior core of the tablet swelled up and by breaking the outer shell rapidly releases the drug[57,58,59].

PRESS-COATED TABLETS - ERODIBLE SHELL



PRESS-COATED TABLETS – GELLABLE SHELL

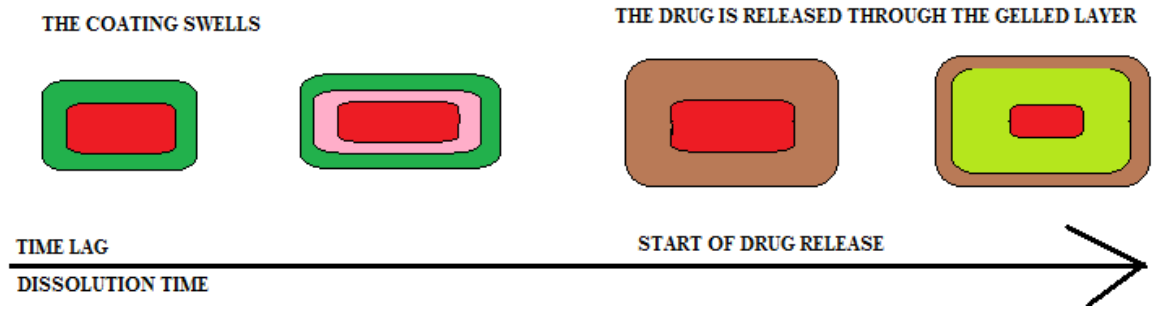


Figure 4: Geometric press coated tablets for delayed release .

1.5.4 Bimodal release profile

In designing of control release system it is considered that the system should release the drug in a zero-order rate, thereby to maintain the plasma drug concentration in a constant level. However, in actual practice for many drugs, absorption is moderately slow in the stomach, rapid in the proximal intestine, and gradually lowered in the distal segment of the intestine. Hence to design constant drug absorption, the dosage form should be able to release the drug in a varying manner, thereby the release can compensate the change in the drug absorption in the different

part of the gastrointestinal tract and provide a control release of the drug. This kind of release pattern can be obtained with the help of bimodal release system. This release system is consisted of an initial rapid release layer, which is then followed by a period of slow and constant release, and again a second phase of rapid drug release[60]. In this delivery system an additional layer known as the fourth layer containing initial dose rapidly disintegrates to produce a quick dissolution onset which ultimately provide a concentration gradient to compensate the poor absorption in stomach. With the help of barrier layers from the sustained release portion drug release is controlled. The pH of the large intestine initiates the second rapid drug release. The advantages of this system over others systems, (i) this dosage form can produces rapid drug release during the initial phase and in the later phase compensate the relatively slow drug absorption in the stomach and large intestine and (ii) it can be used to design programmed pulse release oral drug delivery systems for the therapeutic agents that can perform more effectively or give more therapeutic activity when drug levels at the site of action undergo periodic changes.

1.6 VARIOUS TECHNIQUES FOR BILAYER TABLET

1.6.1. Osmotic-controlled release oral delivery system

In this technology the system is consist of mainly two or three layer among which one or more layer are of the drug and other layers are consist of push layer. The drug layer mainly consists of poorly soluble drug along with diluents, low molecular weight polymer, suspending agent and osmotic agent. The push layer is constructed of a higher molecular weight osmopolymer and an osmagent. A semi permeable membrane surrounds the tablet core. In this technology the medication is sandwiched with an osmotic agent that swells when it takes up water. The sandwich is then coated with a semi permeable membrane .Then a laser is used to drill a tiny hole through the membrane. In the stomach, water passes through the membrane into

the pill, causing the osmotic material to swell, which pushes the drug out of the hole. This delivers the drug to the body at a constant rate instead of all at once, as happens when a traditional pill dissolves. Products manufactured using this technology are Glucotrol Xl and procardia XL both of which are composed of a bilayer tablet core and Concerta is compose of a trilayer tablet core.

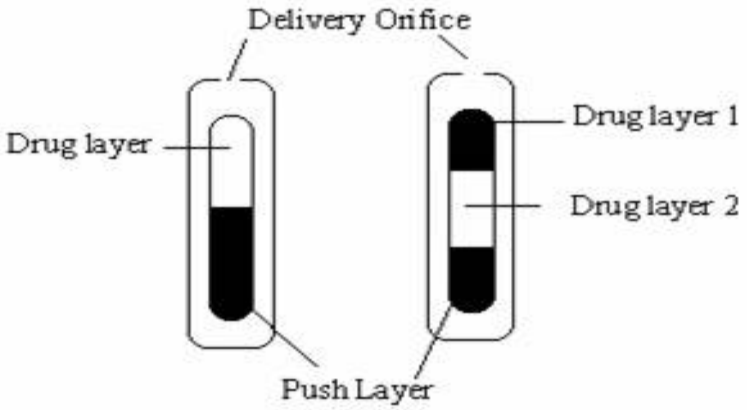


Figure 5: Preparation of bilayer and trilayer tablet

1.6.2 Elan drug technology (DUREDUS technology)

DUREDAS or Dual Release Drug Absorption System (Elan Corporation) utilizes bilayer-tabletting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by two separate direct-compression steps that combine an immediate-release granulate (for rapid onset of action) and a controlled-release hydrophilic matrix complex within one tablet. The immediate release layer, release the drug immediately after going into the GIT (stomach or intestine) in a diffusion and dissolution manner and the controlled-release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix to expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and

the surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner. A further extension of the Duredus technology is the production of controlled-release combination dosage forms whereby two different drugs are incorporated into the different layers, and the drug release of each is controlled to maximize therapeutic effect of the combination. Again both immediate release and controlled release combinations of the two drugs are feasible. The DUREDAS™ technology was initially employed in the development of a number of over the counter controlled release analgesics.

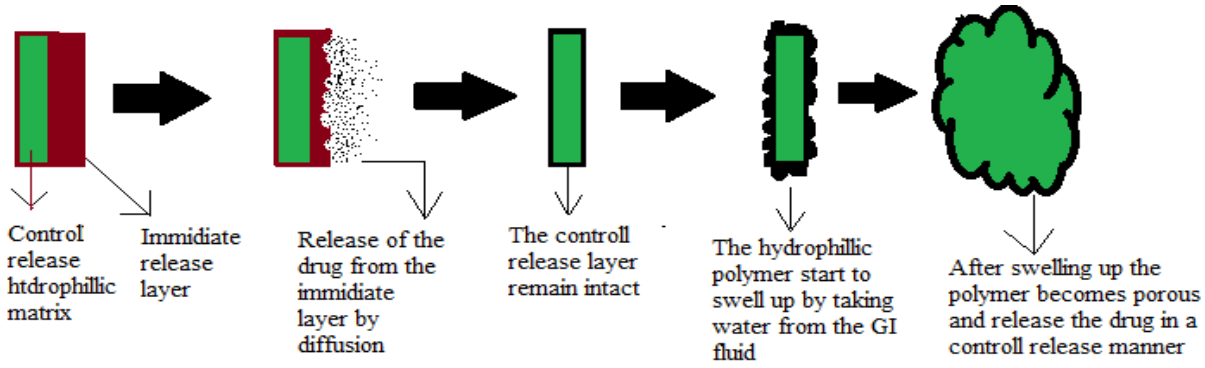


Figure 6: DUREDAS technology consists of control release and immediate release layer.

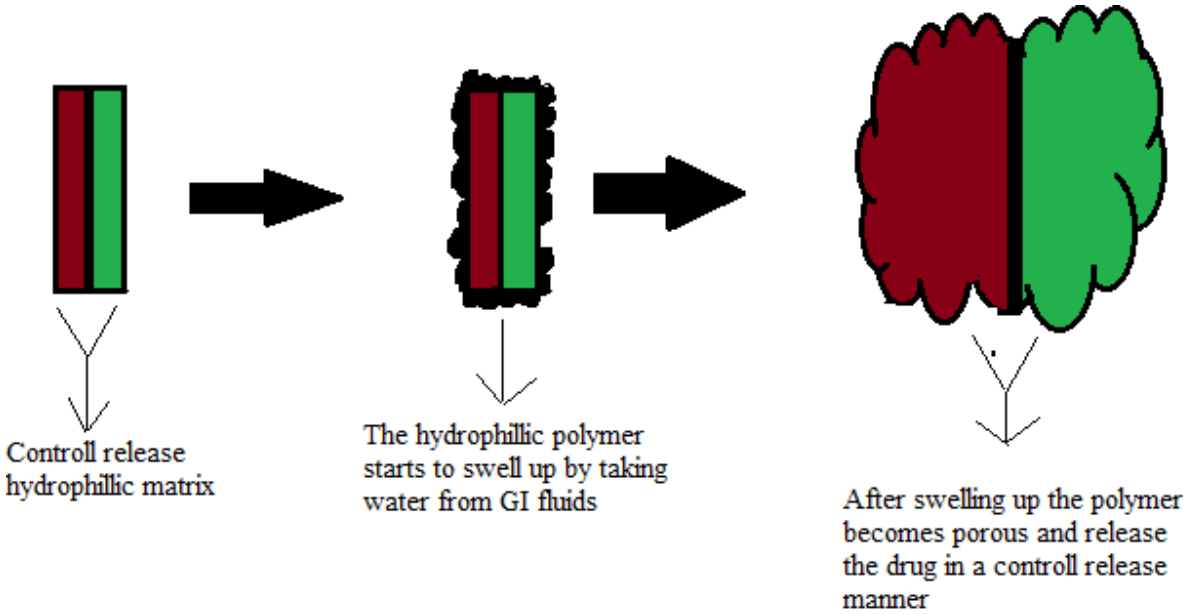


Figure 7: DUREDAS technology consist of two control release layers.

1.7 INFLUENCE OF PROCESS AND FORMULATION PARAMETERS

As the initial dose layer do not affect the intermediate slow release or the second rapid phase or constant phase release, this layer is not necessary to be considered in the formulation process. Multi-layered tablet consisting of a core and one or more barrier layers should be taken into account while determining the parameters involved in the processing. The following factors should be considered for the process and formulation[61,62].

1.7.1 Parameters dealing with the layer consisted of therapeutically active substances

During granulation of therapeutically active substances some basic factors are to be considered which includes percentage of the liquid used in granulation, time required for massing step, temperature of the outlet air during the drying step and milling screen apertures as well as the interaction between the amount of granulation liquid and the outlet temperature [63]. While the impact of these factors on the final products has to be considered and the responses can be classified into four categories: (i) granules properties (e.g., flowability, bulk density, ability to settle, particle size distribution), (ii) extensometric responses (e.g. cohesion index, lubrication index, ejection strength, plasticity, elasticity), (iii) physical characteristics of tablet (e.g. thickness, weight variation, hardness, friability) and (iv) analytical results (e.g. content uniformity, *in vitro* profile).

1.7.2 Compression process

The critical parameters in the compression process are turntable speed and compression forces corresponding to first, second and main layers. The tablet crushing strength response improves when the turret compression speed on the main compression force is increased. But these parameters (within a particular range) do not influence the content uniformity and the release performances in multi-layered, press coated and, bimodal delivery systems[63]. But in the case of press coated tablet intended for distant destination (e.g. colon targeting) the release rate

and lag time are dependent on the compression force. The release rate of drug decreases and the lag time increases with increasing compression force till a critical point. After this point increasing compression force does not provide further reduction in porosity. There is necessity of increasing the lag time more than 10 h in the gastric fluid under some physiological conditions[64] and also there is need for suppression of release in the intestinal fluid for more than 3 h in order to obtain colon targeting. To achieve these certain additives, which have poor wettability, are added to the outer shell polymer to prevent the penetration of dissolution medium into the pores in the outer shell. For example, magnesium stearate or calcium stearate were added to the hydroxyl propyl methyl cellulose acetate succinate (HPMCAS) polymer to increase the lag time. Eiji Fukui *et al.*[58] reported that the drug release in gastric fluid was completely suppressed until 15 h if tablets containing magnesium stearate irrespective of compression force and for tablets containing calcium sterate, it was necessary to increase the compression force to more than the range applied, to suppress until 12 h. In the intestinal fluid the lag time was not prolonged to more than 2 h by addition of magnesium stearate. In contrast lag time could be prolonged by calcium stearate as long as 9 h by increasing the compression force. The above results suggested that press coated tablets intended for colon targeting mainly depends on compression force when poor wettable additives are used.

1.7.3 Hardness of compressed tablet

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in kg/cm^2.

Hardness of tablet is expressed in terms of tensile strength. The tensile strength of the tablet is calculated by the formula, according to Fell and Newton[65].

$$\sigma = \frac{2P}{\pi Dt} \qquad (1)$$

where r = tensile strength (kg/cm^2), D= tablet diameter (cm), t = tablet thickness (cm), P= force applied to fracture (kg). The porosity of the tablets decreased by the rise of tensile strength which is ultimately depends on the compression load. Since the compression force (particular range) does not affects the release rate, therefore, hardness of the tablet (generally in layered construction) has less significance in the formulation.

1.7.4 Polymer concentration in core

Polymer is one of the most important factors that influence the release of drug from the tablets. With the increase of the polymer concentration usually the dissolution rate of the tablet is decreased. This parameter does not affect the drug release in layered tablets as considerably in the bimodal tablet because the solubility of certain polymers depends on the pH of the surrounding medium. For example the effect of decreasing HPMCAS-MF amounts in the inner layer of bimodal delivery system is not significant in pH 1.2 but in pH 7.4 drug release increases with decrease in the amount of polymers[63]. At high pH values a less dense polymer network dissolves more rapidly than a tight structure, leading to increased drug release rate. At low pH HPMCAS-MF is not soluble, thus there is no effect on the breakdown of the polymer network. Therefore, concentration of pH sensitive retard polymers in the core should be controlled more closely.

1.7.5 Filler

Filler used in the core of the tablet, has a great influence on the drug release rate because of its solubility. On contact with the release medium, the filler diffuses out from the device and thereby affect the drug release rate by increasing the porosity of polymers.

Depending upon the amount of the filler the amount of the polymer is adjusted to keep the tablet weight constant. Example of such filler is lactose.

1.8 VARIOUS COMBINATIONS OF BILAYER TABLETS

Table 1 indicates the different formulations of bilayer tablet containing combination of two drug and their specific uses. Table 2 indicates the different formulation of bilayer tablet containing the same drug in both fast release layer and sustained release layer. Table 3 indicates the different bilayer tablet formulation available in the market.

Table 1: Bilayer tablets containing two drugs in an individual layer.

Drug	Drug	Purpose	Ref.
Metformin hydrochloride	Glimepiride	Improve oral therapeutic efficacy with optimal control of plasma drug level	66
Metformin hydrochloride	Pioglitazone	Reduce frequency of administration and improve patient compliance	67
Paracetamol	Diclofenac sodium	Reduce dose frequency and decrease incidence of GI side effects	68
Tramadol	Acetaminophen	Prolonged release up to 12 h and improve patient compliance	69
Salbutamol	Theophylline	Enhance patient compliance and prolong bronchodilation	70
Metoprolol Succinate	Amlodipine besylate	Lower doses of drug to reduce patient blood pressure, minimize dose dependent side effects and adverse reactions	71
Diltiazem hydrochloride	Lovastatin	Improve patient compliance and better disease management	72
Atorvastatin calcium	Nicotinic acid	Develop potential dosage form	73
Metoclopramide hydrochloride	Ibuprofen	Effective treatment of migraine and avoid chemical incompatibility between drugs	74

Table 2: Bilayer tablets containing the same drug in an immediate release layer and sustained release layer.

Drug	Fast release layer/Backing membrane	Sustained release layer	Remarks	Ref.
Indomethacin (Floating tablet)	Ac-di-sol	HPMCK4M	Release the drug from fast release layer within 2h and followed by sustained release for24h.Reduce dose frequency and improve patient compliance	75
Propanolol Hcl (Bucoadhesive tablet)	Ethylcellulose	Sodium alginate and carbopol 971P	Tablets containing sodium alginate and carbopol 971P in the ratio of 5:1 had the maximum percentage of *in vitro* drug release without disintegration in 2 h.	76
Guaifenesin (Matrix tablet)	Microcrystalline cellulose, Sodium starch glycolate	Metalose 90SH, Carbopol 934	Burst release of drug (over 20%) within first half an hour and followed by sustained release for 12 h.	77
Atorvastatin calcium Mucoadhesive buccal tablet)	Ethylcellulose	Carbopol934P, Sodium CMC, Hydroxyethylcellulose,Sodium alginate	The optimized formulation performed 6h sustained drug release with desired therapeutic concentration	78

Propanolol Hcl (Matrix tablet)	Sodium starch glycolate	Ethylcellulose, Eudragit RLPO and Eudragit RSPO	Over 30% of propanolol HCl was released within 15 min and followed by sustained release for 12 h.	79
Zolpidem tartarate (Matrix tablet)	Cross-carmellose sodium	HPMC K100M	Optimized formulation released more than 50% of drug within the first 30min and remaining drug released could be extended upto 6 h.	80
Fenoverine (Floating tablet)	Cross-carmellose sodium	HPMC K4M, HPMC K100LV	Loading dose of the drug was released within 10-15 min and followed by zero-order sustained release upto 12 h.	81
Verapamil hydrochloride (Floating tablet)	Crosspovidone, Sodium starch glycolate	HPMC K15M, HPMC K100M, Carbopol 971P	Immediate release layer get completely dissolved within 15-20 min and 30-45% drug released among the total dose. Concurrently floating sustained release layer released the drug upto 12 h.	82

Table 3: Commercially marketed bilayer tablets

Product Name	Chemical Name	Developer
ALPRAX PLUS	Sertraline, Alprazolam	Torrent Pharmaceutcals Ltd.
Glycomet®-GP2Forte	Metformin hydrochloride, Glimepiride	USV Limited
Newcold Plus	Levocetrizine hydrochloride, Phenylpropanolamine, Paracetamol	Piramal Healthcare Ltd.
DIAMICRON®XRMEX500	Gliclazide,Metformin hydrochloride	Sedia® Pharmaceuticals (India) Pvt. Ltd.
DIUCONTIN-K®20/250	Furosemide,Potassium chloride	T.C. Health Care Pvt. Ltd.
Tribet-1	Glimepiride, Pioglitazone hydrochloride, Metformin hydrochloride	Abbott Healthcare Pvt. Ltd.
Revelol®-Am 25/5	Metoprolol succinate, Amlodipine besilate	Ipca Laboratories Ltd.
PIOKIND®-M15	Pioglitazone, metformine hydrochloride	Psychotropics India Ltd.
TRIOMUNE 30	Nevirapine, Lamivudine, Stavudine	Cipla Ltd.

Review of Literature

2.REVIEW OF LITERATURE

1.Bhavesh S *et al* (2008)bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Bi-layer tablet was suitable for preventing direct contact of these two drugs and thus to maximize the efficacy of combination of two drugs for any dieseas[83].

2. Nagaraju R *et al*(2009) bilayer tablets are novel drug delivery systems where combination of two or more drugs in a single unit having different release profiles which improves patient compliance, prolongs the drug(s) action, avoid saw tooth kinetics resulting in effective therapy along with better control of plasma drug levels. Bi-layer tablets are very common for drugs such as captopril, metoprolol, amoxicillin and potassium clavulanate, propranalol hydrochloride, bambuterol hydrochloride[84] etc

3. Saleh MAS *et al* (2005)the study was to develop guar gum matrix tablets for oral controlled release of water-soluble diltiazem hydrochloride. In pharmaceuticals, guar gum is used in solid dosage forms as a binder and disintegrant. Guar gum is a nonionic polysaccharide. Matrix tablets containing 2 different proportions of various viscosity grades of guar gum were prepared by wet granulation method find the utility of guar gum in providing controlled release. The guar gum matrix tablet formulation providing an optimal in vitro drug release was subjected to further studies to investigate its in vivo performance in healthy volunteers. and subjected to in vitro drug release studies[85].

4.Chinam np *et al* (2007) the objective of the present research was to develop a bilayer tablet of propranolol hydrochloride using super disintegrant sodium starch glycolate for the fast release layer and water immiscible polymers such as ethylcellulose, Eudragit RLPO and Eudragit RSPO for the sustaining layer. In vitro dissolution studies were carried out in a USP 24 apparatus Statistical analysis (ANOVA) showed no significant difference in the cumulative amount of drug release after 15 min, but significant difference ($p < 0.05$) in the amount of drug released after

12 hours from optimized formulations was observed[86].

5. Faith A *et al* (2010)hydrophilic matrix formulations are important and simple technologies that are used to manufacture sustained release dosage forms. Method, Hydroxypropyl methylcellulose-based matrix tablets, with and without additives, were manufactured to investigate the rate of hydration, rate of erosion, and mechanism of drug release. The results revealed that the rate of hydration and erosion was dependent on the polymer combination(s) used, which in turn affected[87] .

6. Uttam M *et al* (2008) the emerging new fixed dose combination of Metformin hydrocholride as sustained release and glipizide as immediate release were formulated as a bilayer matrix tablet using hydroxy propyl methyl cellulose (HPMC) as the matrix-formingpolymer, and the tablets were evaluated via in vitro studies.The release kinetics of metformin were evaluated using theregression coefficient analysis. Tablet thus formulated provided sustained release of metformin HCl over a period of 8 hours and glipizide as immediate release[88]**.**

7. Raghuram RK *et al* (2003)the present study was to develop once-daily sustained-release matrix tablets of nicorandil, a novel potassium channel opener used in cardiovascular diseases. The tablets were prepared by the wet granulation method. Ethanolic solutions of ethylcellulose (EC), Eudragit RL-100, Eudragit RS-100, and polyvinylpyrrolidone were used as granulating agents along with hydrophilic matrix materials like hydroxypropyl methylcellulose (HPMC), sodium carboxy methyl cellulose, and sodium alginate. The results of dissolution studies indicated that formulation F-I (drug-to-HPMC, 1:4; ethanol as granulating agent) could extend the drug release up to 24 hours. In the further formulation development process, F-IX (drug-to-HPMC, 1:4; EC 4% wt/vol as granulating agent), the most successful formulation of the study, exhibited satisfactory drug release in the initial hours, and the total release pattern was very close to the theoretical re-lease profile[89].

8. Anna K *et al* (2009)the effect of three different types of polymer chain structures on the polymer release from hydrophilic matrix tablets was investigated by comparing a synthetic semicrystalline linear polymer (PEO), a branched amorphous polysaccharide (dextran) and an amorphous substituted cellulose derivative (HPMC). The polymer release rates for tablets was

determined by using a modified USP II method and a SEC-RI chromatography system. This confirms the hypothesis that the release rate can be related to a constant viscosity on the surface of the hydrophilic matrix tablet and that it is valid for all the investigated polymers[90].

9. Jose MCB *et al* (2010)poly(carboxyalkyl methacrylates) were studied as a cationic-drug delivery system, at pH 6.8 and 8.0. Different polymer/ drug complexes were used to prepare compressed tablets. By kinetics experiments, we have found that drug releaseis dependent on both the hydrophobicity of the whole complex and the pH of the environment. Furthermore, amechanism of dissociation/erosion clearly describes the drug release from a complex formed by a polymer solubleat target pH; otherwise, a mechanism of dissolution/diffusion is depicted. Since our results using different polymer/drug complexes exhibitpH-sensitive drug release, we propose that the poly(carboxyalkyl methacrylates) have potential as a colon-specificdrug-delivery system.[91]

10. Vanna S *et al* (2004) the study was the preparation of bilayer tablets asrumen-stable delivery systems, designed for the oral administration of active ingredients (folic acid) to ruminants. In vitro rumen-protection tests were performed in buffer systems at pH 5.5 and pH 2.0, simulating a ruminal and abomasal environment, to verify the stability of bilayer tablets at these conditions. The tablets having layer B constituted by poly (e-caprolactone) or Eudragit RS do not disintegrate in buffer media at pH 5.5 and pH 2.0, and they are characterized by a sustained release at pH 7.4. Radiological preliminary tests show that these prepared bilayer tablets are able to be retained in the reticulum–rumen tract of the sheep[92]

11. Mukesh G *et al* (2009) this research work was to develop venlafaxine hydrochloride-coated and layered matrix tablets using hypromellose adopting wet granulation technique. The granules and the tablets were characterized. The monolithic tablets were coated with different ratios of ethyl cellulose and hypromellose. The invitro dissolution study was performed in distilled water. The monolithic tablets were coated with different ratios of ethyl cellulose and hypromellose. The invitro dissolution study was performed in distilled water. The layered tablets also exhibited sustained release without burst effect due to effective area reduction. Layered tablets may well be adopted by the industry due to the possibility of achieving a highproduction rate[93]

12. Yassin El-Said H *et al* (2010) the proposed strategy was based on preparing directly

compressed hydroxypropylmethylcellulose matrix tablets to sustain lornoxicam release. Basic pH-modifiers, either sodium bicarbonate or magnesium oxide, were incorporated into these matrix tablets to create basic micro-environmental pH inside the tablets favorable to drug release in acidic conditions. All the prepared matrix tablets containing basic pH-modifiers showed acceptable physical properties before and after storage. Release studies,performed in simulated gastric and intestinal fluids used in sequence to mimic the GI transit, demonstratethe possibility of sustaining lornoxicam release by combining hydrophilic matrix formers and basic pH Modifiers to prepare tablets that meet the reported sustained-release specifications[94]

13. Chuan-Yu Wu *et al* (2009)the compaction behaviour of binary mixtures and bilayer tablets of two common pharmaceutical excipients, Microcrystalline cellulose and lactose, is investigated. The effects ofcompositions and compaction pressure on the compaction behaviour of binary matrix mixtures and bilayer tablets are also explored. The delamination phenomena during the manufacturing of bilayer tablets and fracture patterns of tablets subjected to diametrical compression are examined using X-ray computed tomography. It was also found that, using the same compaction process, the relative densities of the tablets were generally different when different compositions were used, especially when the maximum compression pressure is relatively low[95].

14. Harikrishna B *et al* (2009) matrix tablet formulation has been used to develop controlled release diltiazem HCl tablets..The developed drug delivery system provided prolonged drug release rates over a defined period of time.DIL tablets prepared using dry mixing and direct compression and the core consisted of hydrophilic and hydrophobic polymers such as hydroxypropylmethylcellulose, Eudragits RLPO/RSPO, microcrystalline cellulose, and lactose. The release profile of the developed formulation was described by the Higuchi model. Stability trials up to 6 months displayed excellent reproducibility[96].

15. S.Mohamed Halith *et al* (2011), Formulated and evaluated of bilayer tablets of amlodipine besilate and metprolol succinate and have done on DSC studies formulation and compare to pure compound Heat flow rates were measured over a temperature range of 30°C - 300°C at a heating rate of 15°C/min for Amlodipine Besilate pure drug, placebo and tablet samples. Similarly temperature range of 25°C- 250°C at a heating rate of 5°C/min was used for

Metoprolol Succinate pure drug, placebo, and tablet samples[97].

16. Vaijanath G. ***et al,.(*2008)** Simultaneous determined metoprolol succinate and amlodipine besylate in pharmaceutical dosage form by HPLC. The mobile phase consisting of buffer (aqueous triethylamine pH 3) and acetonitrile in the ratio of 85: 15 (v/v) at a flow rate of 1.0 ml/min was used. The method was validated according to the ICH guidelines with respect to specifity, linearity, accuracy, precision and robustness[98].

17. Prasada Rao *et al*., (2010)developed a simple, rapid and selective HPLC method developed for quantization of Amlodipine Besylate and Metoprolol succinate from bulk drug and pharmaceutical formulations using a mobile phase consisting mixture of 0.02 M phosphate buffer solution and Acetonitrile as 80:20 at the flow rate of 1 mL/min. An Inertsil ODS-CV column was used as stationary phase. The retention time of Amlodipine Besylate and Metoprolol succinate were 3.92 and 10.43 respectively[99]

18. V.Rajamanickam *et al.,(2010)* developed and validate a economic, rapid reversed-phase high-performance liquid chromatographic method for the quality control of Metoprolol succinate and amlodipine besylate in pharmaceutical preparations with lower solvent consumption along with the short analytical run time leads to an environmentally friendly chromatographic procedure that allows the analysis of a large number of samples in a short period of time[100].

19. N.N.Rajendran *et al,(2010)* investigated the effect of a novel drug- drug solid dispersion approach on the dissolution of hydrochlorothiazide in a fixed dose combination with Losartan potassium Solid dispersions by differential scanning calorimetry, x-ray diffractometry and dissolution tests and the results were compared with that of pure drugs and physical mixtures. Solid dispersion as well as physical mixture were then compressed into tablets and evaluated for physicochemical, stability and dissolution characteristics and the results compared with commercial tablets[101].

20. Chuan-Yu *et al.,(2009)* described the compaction behavior of binary mixtures andbilayer tablets of two common pharmaceutical excipients, microcrystalline cellulose and lactose. Thedelamination phenomena during the manufacturing of bilayer tablets and fracture patterns of tablets subjected to diametrical compression are examined using X-ray computed to monography. The mechanical properties of binary and bilayer tablets of the same composition

were also determined and compared[102].

21. **Jakkie *et al.,(1997)*** reported the effect of V-mixer size on the mixing of magnesium stearate with directly compressible microcrystalline cellulose and evaluated the mixing process and compare the performance of the mixers, the extent of the decrease in tablet crushing strength was measured. The kinetics of the decrease in crushing strength were best described by the sum of two separate processes, one first-order and the other second-order. Overall, the faster second-order process dominated mixing because the first-order rate decreased, while the second-order rate increased. with an increase in mixer volume. Results showed that the limiting crushing strength increased with an increase in mixer size and that there was a linear relationship between the limiting crushing strength and the logarithm of the volume of the mixer. A decrease in mixer load from 33 to 18% also led to an decrease in tablet strength[103].

22. **Calum *et al***.,(2002) developed bilayer mucoadhesive tablets of Nicotine evaluated to determine the suitability of the formulation as a Nicotine replacement product to aid in smoking cessation. A combination of 20% w/w carbopol 934 and 20% w/w Hydroxypropylcellulose was found to provide suitable adhesion and controlled drug release. The formulation of bilayer tablet containing the adhesive controlled release layer and a fast releasing layer provided an initial burst release of drug followed by the controlled release for a period of upto 4 hours[104].

23. Miyazaki *et al*.,(2000) developed potential of bilayer tablets containing 1:4, 1:1 and 4:1 weight ratios of pectin and HPMC for the sustained release of Diltiazem by sublingual administration has been investigated. An *in vitro* sustained release of Diltiazem over 5 hours was achieved with bilayer tablets composed of a drug-free ethyl cellulose layer in addition to the pectin/HPMC layer containing drug. Bioavailability of Diltiazem was 2.5 times than achieved by oral administration for single layer tablets and 1.8 time for the bilayer tablets[105].

24. Anil Chaudhary *et al.,(2011)* prepared microporous bilayer osmotic tablet bearing dicyclomine hydrochloride and diclofenac potassium by using a new oral drug delivery system for colon targeting. The tablets were coated with microporous semi permeable membrane and enteric polymer using conventional pan-coating process. The number of pores was dependent on the amount pore former in the semi permeable membrane. *In vitro* dissolution results indicated that system showed acid resistance, timed release was able to deliver drug at an approximate zero

order up to 24 hour[106].

25. Carmen *et al.,(1998)* prepared new buccal delivery devices comprising a drug containing mucoadhesive layer and a drug free backing layer, by two different methods. The mucoadhesive layer was composed of a mixer of drug and chitosan, with or without an anionic cross linking polymer (polycarbophill, sodium alginate, gellan gum), and the backing layer was made of ethyl cellulose. The double layered structure design was expected to provide drug delivery in a unidirectional fashion to the mucosa and avoid loss of drug due to wash out with saliva. Using nifedipine and propranolol hydrochloride as slightly and highly water soluble model drugs, respectively, it was demonstrated that show promising potential for use in controlled delivery of drugs to the oral cavity. The uncrosslinked chitosan containing devices absorbed a large quantity of water, jelled and then eroded allowing drug release. The bilaminated films shows a sustained drug release in a phosphate buffer (pH 6.4)[107]

26. Yong Shao *et al.,(2005)* used electrochemically synthesized conducting polymer polypyrrole (PPy) film on gold electrode surface was used as a novel support for bilayer lipid membrane (BLMs). The formation of PPy supported bilayer lipid membranes (s-BLMs) is dependent on the chemical structure of the lipid use[108].

27. Fridrun Podczeck *et al.,(2010)* determined the tensile strength of bilayer tablets made from different grades of microcrystalline cellulose. While these grades are chemically identical, they differ significantly in their particle size distribution and in their mechanical properties such as young's modules of elasticity. Both particle size and Young's modules of elasticity influenced the overall strength of layered tablets. If the material forming the lower layer was more elastic, then the beam strength was reduced due to tension introduced into the system, acting especially at the layer interface and potential causing partial or complete delamination[109].

28. Ajit Kulkarni *et al.,(2009)* Developed of regioselective bilayer floating tablets of Atenolol and Lovastatin for biphasic release profile. In DSC studies *the tablet was ground to powder and a 1-2 mg sample was hermetically sealed in an aluminum pan and heated at a constant rate of 10°C/min, over a temperature range of 50-200 °C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 20 ml/min* d[110].

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29. A. Streubel *et al.,(2010)* developed new multi-layer matrix tablets to achieve bimodal drug release profiles (fast release /slow release / fast release). Hydroxypropyl methylcellulose acetate succinate (HPMCAS, type MF) as a matrix former, because it is water-insoluble at low, and water-soluble at high pH values. The addition of a fourth, drug-containing and fast disintegrating initial dose layer yielded the desired bimodal drug release patterns. The process and formulation parameters affecting the resulting release rates using theophylline and acetaminophen as model drugs[111].

30. Rashmi Dahima *et al.(2010)* increased the solubility and dissolution rate of amlodipine besylate by the preparation of its solid dispersion with cross povidone using solvent evaporation method. Drug polymer interactions were investigated using differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR). Surface morphology of solid dispersion particle determined by SEM study. Dissolution rate of solid dispersion was determined in 0.01 N HCl at 75 rpm. The obtained results showed that dispersion of the drug in the polymer considerably enhanced the dissolution rate. It revealed that crosspovidone in solid dispersion itself act as superdisintegrant and binder and an optimum concentration of a pregelatinized starch is required for obtaining rapidly disintegrating tablets. The potential of experimental design in understanding the effect of the formulation variables on the quality of mouth dissolving tablets containing solid dispersion of a hydrophobic drug[112].

31. Naeem *et al*.,(2010) developed and characterized bilayer tablet formulations of tramadol HCl (TmH) and acetaminophen (AAP) microparticles. Coacervation via temperature change the encapsulated method used for the preparation of the microparticles, with ethyl cellulose (EC) of medium viscosity as the polymer for extending drug release. FTIR, XRD, DSC and TGA data for the formulations indicate good compatibility and stability. Furthermore, accelerated stability studies confirmed the stability of the formulations. Controlled drug release from the microparticles and bilayer tablets was observed for 8 h and 12h, respectively. Microencapsulated TmH and AAP can be developed into suitable bilayer tablets that are stable and capable of releasing the drugs over 12hours[113].

32. L. Yang *et al.,(1997)* formulated components were poly(ethylene oxide) (PEO), lactose, and theophylline. Results indicate that the formulation of each layer and the combined triple-layer tablet exhibited similar compression behavior, and the consolidation mechanism was shown to follow predominantly plastic deformation as evidenced by the shape of Heckel plots and high SRS (Strain Rate Sensitivity) values. A triple-layer tablet formulation necessitates careful selection of plastic, brittle, and other desirable components to ensure comparable compactibility profiles[114].

Aim and Plan of work

3.AIM AND PLAN OF WORK

The aim of the present study is to formulate and evaluate film coated tablets of Amlodipine besylate and Losartan Potassium. The work will be scheduled as:

1. To develop suitable analytical method for the estimation of the drug.
2. To Perform Preformulation studies
3. Formulation and evaluation of Bilayer tablets:
    - Formulation of Immediate- release granules of Amlodipine Besylate.
    - Formulation of Immediate-release granules of Losartan Potassium.
    - Evaluation of Immediate- release granules of Amlodipine Besylate
    - Evaluation of Immediate-release granules of Losartan Potassium.
    - Compression of bilayer tablets.
    - Evaluation of compressed Bilayer tablets
4. Optimization of formulation parameters and drug-carrier system using appropriate methods.
5. Stability studies of the most satisfactory formulation will be carried out as per ICHguidelines.

Drug Profile

4.DRUG PROFILE

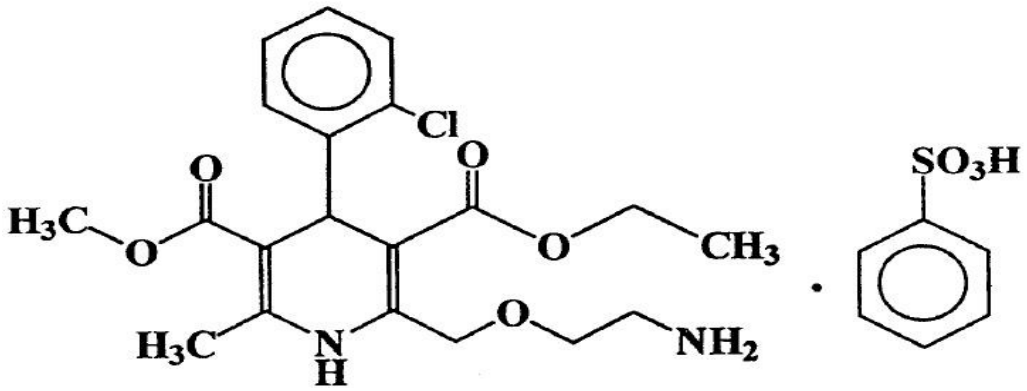
Amlodipine Besylate[115,116]

Category : Cardio vascular agent , calcium channel blocker

Empirical Formula : $C_{20}H_{25}$ cl N_2O_5

Molecular Weight : 408.876

Structure Formula:



Chemical Name: 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-1, 4-dihydro-6-methyl-3, 5-pyridinedicarboxylate, monobenzenesulphonate

Physiochemical Properties

Appearance, odour and Colour: A white or almost white powder.

Melting Point: 195 - 204 C

Solubility: Slightly soluble in water, freely soluble in methanol; sparingly soluble in anhydrous ethanol, slightly soluble in 2-orooanol.

PHARMACODYNAMICS

Amlodipine belongs to the dihydropyridine (DHP) class of calcium channel blockers (CCBs), the most widely used class of CCBs. There are at least five different types of calcium channels in Homo sapiens: L-, N-, P/Q-, R- and T-type. It was widely accepted that DHP CCBs . .

target L-type calcium channels, the major channel in muscle cells that mediate contraction; however, some studies have indicated that Model drug 1 also binds to and inhibits N-type calcium channels. Similar to other DHP CCBs, Model drug 1 binds directly to inactive L-type calcium channels stabilizing their inactive conformation. Since arterial smooth muscle depolarizations are longer in duration than cardiac muscle depolarizations, inactive channels are more prevalent in smooth muscle cells. Alternative splicing of the alpha-1 subunit of the channel gives GEN001 additional arterial selectivity. At therapeutic sub-toxic concentrations,Amlodipine has little effect on cardiac myocytes and conduction cells.

MECHANISM OF ACTION

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that Model drug binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by Model drug. Within the physiologic pH range, Amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Biological Properties

cLogP	:	3.43400
LogP	:	2.0
pKa	:	8.6
Cmax	:	5.14 ng/ml
T max	:	6 – 12 hours
Half-life (Mean)	:	30-50 hours

Pharmacokinetics

Absorption:

Amlodipine is slowly and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations are reached 6-12 hour following oral administration. Its estimated bioavailability is 64-90%. Absorption is not affected by food.

Distribution: Ex vivo studies have shown that approximately 95%of the circulating GEN001s bound to plasma proteins in hypertensive patients.

Metabolism: Hepatic. Metabolized extensively (90%) to inactive metabolites via the cytochrome P450 3A4 isozyme.

Excretion

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.

Dosage: Maximum dose of 10 mg daily.

Contraindications:

Amlodipine (Besylate) is contraindicated in conditions like Aortic Stenosis

PRECAUTIONS:

General:

Since the vasodilation induced by Amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution, as with any other peripheral vasodilator, should be exercised when administering Amlodipine, particularly in patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure:

In general, calcium channel blockers should be used with caution in patients with heart failure. Amlodipine (5 to 10 mg per day) has been studied in a placebo-controlled trial of

1153 patients with NYHA Class III or IV heart failure (see CLINICAL PHARMACOLOGY) on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

Beta-Blocker Withdrawal:

Amlodipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Patients with Hepatic Failure:

Since Amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t 1/2) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering Amlodipine to patients with severe hepatic impairment.

Amlodipine interactions: In vitro data indicate that Amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Effect of other agents on Amlodipine

CIMETIDINE: Coadministration of Amlodipine with cimetidine did not alter the pharmacokinetics of Amlodipine.

GRAPEFRUIT JUICE: Coadministration of 240 mL of grapefruit juice with a single oral dose of Amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of Amlodipine

MAALOX (antacid): Coadministration of the antacid Maalox with a single dose of amlodipine

had no significant effect on the pharmacokinetics of Amlodipine.

Effect of Amlodipine on other agents .

ATORVASTATIN: Co administration of multiple 10 mg doses of Amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

DIGOXIN: Co administration of Amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

ETHANOL (alcohol): Single and multiple 10 mg doses of Amlodipine had no significant effect on the pharmacokinetics of ethanol.

WARFARIN: Co administration of Amlodipine with warfarin did not change the warfarin prothrombin response time.

In clinical trials, Amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

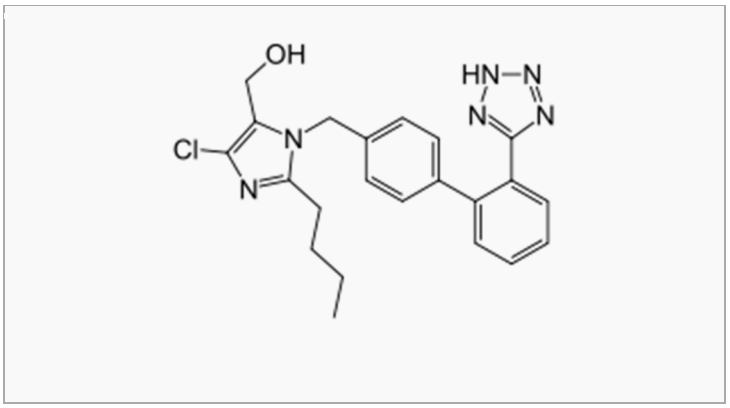
Losartan Potassium[116]

Category **:** Cardio vascular agent , angiotensin II receptor antagonist

Molecular Formula : $C_{22}H_{23}ClN_6O$

Molecular Weight **:422.9**

Structure:



Systematic (IUPAC) name :

(2-butyl-4-chloro-1-{[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1*H*-imidazol-5-yl)methanol

Pharmacodynamics:

Losartan is an Angiotensin II receptor antagonist drug used mainly to treat high blood pressure (hypertension). Losartan was the first angiotensin II receptor antagonist to be marketed. Losartan potassium is marketed by Merck & Co. Inc. under the trade name **Cozaar**. As of 2009, losartan is available in generic form. As with all angiotensin II type 1 receptor (AT_1) antagonists, losartan is indicated for the treatment of hypertension. It may also delay progression of diabetic nephropathy, and is also indicated for the reduction of renal disease progression in patients with type 2 diabetes, hypertension and microalbuminuria (>30 mg/24 hours). Although clinical evidence shows calcium channel blockers and Thiazide-type diuretics are preferred first-line treatments for most patients (from both efficacy and cost points of view), an angiotensin II

receptor antagonist such as losartan is recommended as first-line treatment in patients under the age of 55 who cannot tolerate an ACE inhibitor. The LIFE study demonstrated losartan was significantly superior to atenolol in the primary prevention of adverse cardiovascular events (myocardial infarction or stroke), with a significant reduction in cardiovascular morbidity and mortality for a comparable reduction in blood pressure. A study hints that losartan has a beneficial effect on mitochondria by reversing age related dysfunction in maintaining normal blood pressure and cellular energy usage. The maximal effects on blood pressure usually occur within 3-6 weeks upon starting losartan.

Losartan is also available as hydrochlorothiazide/losartan, a combination drug with a low dose thiazide diuretic to achieve an additive antihypertensive effect.

Mechanism of action:

Losartan is a selective, competitive angiotensin II receptor type 1 (AT_1) receptor antagonist, reducing the end organ responses to angiotensin II. Losartan administration results in a decrease in total peripheral resistance (afterload) and cardiac venous return (preload) All of the physiological effects of angiotensin II, including stimulation of release of aldosterone, are antagonized in the presence of losartan. Reduction in blood pressure occurs independently of the status of the renin-angiotensin system. As a result of losartan dosing, plasma renin activity increases due to removal of the angiotensin II feedback.

Pharmacokinetics:

Losartan is well absorbed following oral administration and undergoes significant first-pass metabolism to produce 5-carboxylic acid metabolite, designated as EXP3174. This metabolite is a long-acting (6 to 8 hr), noncompetitive antagonist at the AT_1 receptor, and contributes to the pharmacological effects of losartan. EXP3174 is 10-40 times more potent in blocking AT_1 receptors than losartan. Losartan's bioavailability is about 32%. Metabolism is primarily by cytochrome P450 isoenzymes CYP2C9 and CYP3A4. Peak plasma concentrations of losartan and E-3174 occur about one hour and three to four hours, respectively, after an oral dose. Both losartan and E-3174 are more than 98% bound to plasma proteins. Losartan is excreted in the urine, and in the feces via bile, as unchanged drug and metabolites. About 4% of an oral dose is excreted unchanged in urine, and about 6% is excreted in urine as the active metabolite. The terminal elimination half lives of losartan and E-3174 are about 1.5 to 2.5 hours and 3 to 9 hours, respectively.

Excipients Profile

5. EXCIPIENTS PROFILE

6.1 Hydroxypropyl MethylCellulose[117]

Synonyms: Hydroxypropylmethylcellulose;HPMC;Methocel;Benecel MHPC
methyl hydroxy propyl cellulose; methylcellulose propylene glycol ether; Metolose.

Structural formula:

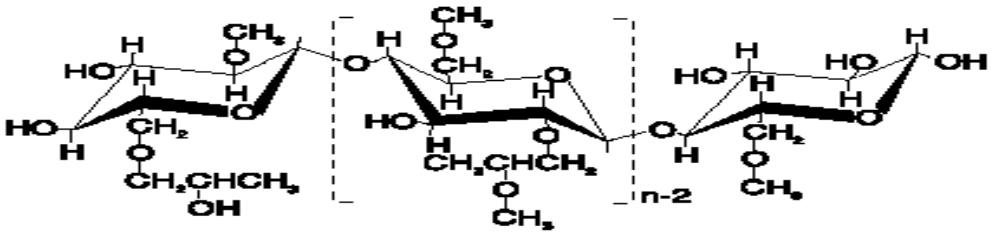


Figure: 7 Structure of HPMC

Functional category:

Coating agent, film-former, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

Physicochemical Properties:

Description	:	White to off white powder, free flowing powder
Particle size	:	Minimum 95% through a #40 US standard sieve
Methoxyl content	:	19-24%
Hydroxypropyl content	:	7-12%
Bulk density	:	0.12 – 0.15 g/ml
pH (1% content)	:	5.5-8

Solubility : HPMC K100M is a high viscosity polymer which is soluble in water.

Stability and storage:

Hypromellose powder is stable material, although it is hygroscopic after drying. Solutions are stable at PH 3-11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol-gel transformation upon heating and cooling. The gel point is 50-90^{0}C, depending upon the grade and concentration of material.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long term storage. However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking. Hypromellose powder should be stored in a well closed container, in a cool, dry place.

Applications:

Hypromellose is primarily used as a tablet binder, in film coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation process. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10-80% w/w in tablets and capsules. Hypromellose is also used as suspending agent in topical formulations. Compared with methyl cellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fiber present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45-1.0% w/w may be added as thickening agent to vehicles for eye drops and artificial tear solutions.

Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.

6.2 Sodium Starch Glycolate[118]

Synonyms:

Carboxymethyl starch, Explotab, Primojel.

Functional Category:

Tablet and capsule disintegrant.

Description:

It is white to off-white, odourless, tasteless, free-flowing powder.

Solubility

It is practically insoluble in water; sparingly soluble in ethanol (95%). In water it swells upto 300 times its volume.

Incompatibilities

Incompatible with ascorbic acid

Stability and Storage

It is a stable material. It should be stored in a well closed container to protect from wide variations in humidity and temperature that may cause cracking.

Safety

It is generally regarded as a non-toxic and non-irritant material. However, oral ingestion of large quantities may be harmful.

Applications in Pharmaceutical Formulation and Technology:

As a disintegrant in tablet (wet granulation and direct compression) and capsule formulation in 2-8% concentration

6.3 Colloidal Silicone Dioxide (Aerosil)[119]

Nonproprietary Names

BP	:	Colloidal anhydrous silica
PhEur	:	Silica colloidalis anhydrica
USPNF	:	Colloidal silicon dioxide
Synonyms	:	colloidal silica, fumed silica, light anhydrous silicic acid, silicic anhydride and silicon dioxide fumed
Chemical Name	:	Silica
Molecular Weight	:	60.08
Structural Formula	:	SiO_2

Functional Category:

Adsorbent, anticaking agent,emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer, and viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Its small particle size and large specific surface area gives desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tabletting.

Description

Colloidal silicon dioxide is submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, and non-gritty amorphous powder.

Stability and Storage Conditions

Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0-7.5, colloidal silicon dioxide is

effective in increasing the viscosity of a system. However, at a pH greater than 7.5 the viscosity-increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates. Colloidal silicon dioxide powder should be stored in a well-closed container. Some grades of colloidal silicon dioxide have hydrophobic surface treatments that greatly minimize their hygroscopicity.

6.4 Crospovidone[120]

Non proprietary Names:

BP : Crospovidone, PhEur : Crospovidonum, USPNF : Crospovidone

Synonyms :

Crosspovidonum ; crospopharm ; croslinked povidone; polyplasdone XL ;

Polyvinyl polypyrrolidine.

Chemical name : 1 – ethenyl – 2 - pyrrolidine homopolymer.

Description:

Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odourless or nearly odourless, hygroscopic powder.

Applications in Pharmaceutical Formulation:

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2-5% concentration in tablets prepared by direct compression or wet and dry-granulation methods. It is rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs.

Moisture Content : Maximum moisture sorption is approximately 60%.

Solubility : Practically insoluble in water and most common organic solvents.

Incompatibilities:

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adduct with some materials like sulfathiazole, sodium salicylate, salicylic acid, Phenobarbital and tannin.

6.5 Micro Crystalline Cellulose[121]

Non Proprietary Names:

BP : Microcrystalline Cellulose

JP : Microcrystalline Cellulose

PhEur : Cellulose, Microcrystalline

USP-NF : Microcrystalline Cellulose

Synonyms :

Avicel PH; Celex; Cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; ethispheres .

Description :

Microcrystalline cellulose is a purified partially depolymerised cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Chemical Name : cellulose

Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ 36000
where n=220

Functional Category :

Adsorbent; suspending agent; tablet and capsule diluents; tablet disintegrant.

Stability and Storage Conditions

Microcrystalline cellulose is a stable through hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities : Microcrystalline cellulose is a incompatible with strong oxidizing agents.

Applications:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluents in oral tablet and capsule formulations where it is used in both wet granulation and direct-compression processes. In addition to its use as a binder/diluents, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

6.6 Starch[122]

Nonproprietary Names

Maize starch, Potato starch, Rice Starch, Tapioca Starch, Wheat Starch (BP, JP, PhEur, USP)

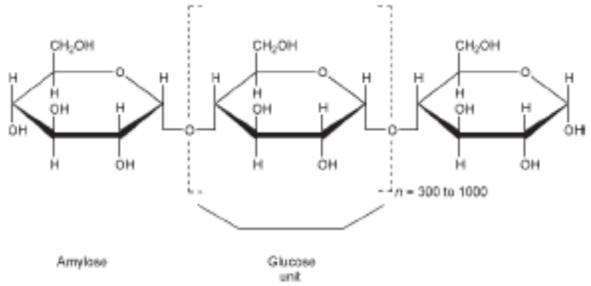
Synonyms

Amido, amidon, amilo, amylum, C*PharmGel, Eurylon, fecule, Hylon, maydis amylum, Melojel, Meritena, oryzae amylum, Pearl, Perfectamyl, pisi amylum, Pure-Dent, Purity 21, Purity 826, solani amylum, tritici amylum, Uni-Pure.

Empirical Formula : $(C_6H_{10}O_5)_n$ where n = 300–1000.

Molecular Weight : 50 - 500 million Da

Structural Formula



Description

Starch occurs as an odorless and tasteless, fine, white to off-white powder. It consists of very small spherical or ovoid granules or grains whose size and shape are characteristic for each botanical variety.

Typical Properties

pH : 4.0–8.0

Moisture content:

All starches are hygroscopic and absorb atmospheric moisture to reach the equilibrium humidity. The approximate equilibrium moisture is 12 – 18 %

Solubility :

Practically insoluble in cold ethanol (96%) and in cold water. Starch becomes soluble in hot water at temperatures above the gelatinization temperature. Starches are partially soluble in dimethylsulfoxide and dimethylformamide.

Functional Category:

Tablet and capsule diluent; tablet and capsule disintegrate; tablet binder; thickening agent.

Applications in Pharmaceutical Formulation or Technology:

Starch act as an antiadherent and lubricant in tableting and capsule filling (3–10% w/w).In tablet formulations, freshly prepared starch paste is used at a concentration of 3–20% w/w (usually 5–10%, depending on the starch type) as a binder for wet granulation. Starch is one of the most commonly used tablet disintegrants at concentrations of 3–25% w/w;a typical concentration is 15%.Starch, particularly the fine powders of rice and wheat starch, is also used in topical preparations for its absorbency of liquids. Starch paste is used in ointment formulations, usually in the presence of higher ratios of glycerin. Starch has been investigated as an excipient in novel drug delivery systems for nasal, and other site-specific delivery systems (colon). They can improve the bioavailability of poorly soluble drugs. Starch has also been used in the treatment of children's diarrheal diseases. Starches with a high amylopectin content (waxy starches) are used as the starting material for the synthesis of hydroxyethyl starch, a plasma volume expander.

Stability and Storage Conditions:

Dry starch is stable if protected from high humidity.Starch should be stored in an airtight container in a cool, dry place

Incompatibilities:

Starch is incompatible with strongly oxidizing substances. Colored inclusion compounds are formed with iodine.

Safety:

It is regarded as an essentially nontoxic and nonirritant material. Both amylose and amylopectin have been evaluated as safe and without limitation for daily intake.

6.7 Isopropyl Alcohol [123]

Nonproprietary Names:

Isopropyl Alcohol (BP, JP, PhEur, USP)

Synonyms:

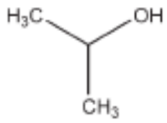
Alcohol isopropylicus, dimethyl carbinol, IPA, isopropanol, petrohol, 2-propanol, sec-propyl

Chemical Name : Propan-2-ol

Empirical Formula : C_3H_8O

Molecular Weight : 60.1

Structural Formula



Description

Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor and it has a slightly bitter taste.

Typical Properties

Boiling point : 82.4^0C

Flammability : Flammable.

Viscosity (dynamic) : 2.43 mPas at 20^0C

Specific gravity : 0.786

Solubility

Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone; insoluble in salt solutions.

Functional Category: Disinfectant, solvent.

Applications in Pharmaceutical Formulation or Technology

Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation, where the isopropyl alcohol is subsequently removed by evaporation. It has also been shown to significantly increase the skin permeability of nimesulide. Isopropyl alcohol has some antimicrobial activity and a 70% v/v aqueous solution is used as a topical disinfectant. Therapeutically, isopropyl alcohol has been investigated for the treatment of postoperative nausea or vomiting.

Storage Conditions

Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

Incompatibilities

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid,

which cause decomposition.

Safety:

Isopropyl alcohol is most frequently used in topical pharmaceutical formulations where it may act as a local irritant. When applied to the eye it can cause corneal burns and eye damage.

6.8 Magnesium stearate[124]

Description:

It is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

Molecular weight	:	591.34
Structural Formula	:	$[CH3 (CH_2)_{16} COO]_2 Mg$
Crystalline Forms	:	High purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.
Flow ability	:	Poorly flowing, cohesive powder.
Melting range	:	117-150 ^oC (commercial samples) 126-130 ^oC (high purity magnesium stearate)
Solubility	:	Practically insoluble in ethanol, ether and water; slightly soluble in warm benzene and warm ethanol (95 %)
Functional category	:	Tablet and capsule, lubricant.
Applications	:	It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0 % w/w.
Incompatibilities	:	Incompatible with strong acids, alkalis, and iron salts. Strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins and most alkaloidal salts.
Safety	:	Oral consumption of large quantities may result in some laxative effect or mucosal irritation

6.9 Dibasic Calcium Phosphate[125]

Nonproprietary Names

BP: Calcium hydrogen phosphate
JP: Dibasic calcium phosphate
PhEur: Calcii hydrogenophosphas dihydricus
USP: Dibasic calcium phosphate

Synonyms

Calcium hydrogen orthophosphate dihydrate; calcium monohydrogen phosphate dihydrate; Di-Cafos; dicalcium orthophosphate;DI-TAB; E341; Emcompress; phosphoric acid calcium salt (1 : 1) dihydrate; secondary calcium phosphate.

Chemical Name and CAS Registry Number

Dibasic calcium phosphate dihydrate

Functional Category

Tablet and capsule diluent.

Applications in Pharmaceutical Formulation or Technology:

Dibasic calcium phosphate dihydrate is widely used in tablet formulations both as an excipient and as a source of calcium and phosphorus in nutritional supplements.(1–8) It is one of the more widely used materials, particularly in the nutritional/health food sectors. It is also used in pharmaceutical products because of its compaction properties, and the good flow properties of the coarse-grade material. The predominant deformation mechanism of dibasic calcium phosphate coarsegrade is brittle fracture and this reduces the strain-rate sensitivity of the material, thus allowing easier transition from the laboratory to production scale. However, dibasic calcium phosphate dihydrate is abrasive and a lubricant is required for tableting, for example about 1% w/w of magnesium stearate or about 1% w/w of sodium stearyl fumarate is commonly used. Two main particle-size grades of dibasic calcium phosphate dihydrate are used in the pharmaceutical industry. The milled material is typically used in wet-granulated, roller-compacted or slugged formulations. The ‘unmilled’ or coarse-grade material is typically used in direct-compression formulations.Dibasic calcium phosphate dihydrate is non

hygroscopic and stable at room temperature. However, under certain conditions of temperature and humidity, it can lose water of crystallization below 1008C. This has implications for certain types of packaging and aqueous film coating since the loss of water of crystallization appears to be initiated by high humidity and by implication high moisture vapor concentrations in the vicinity of the dibasic calcium phosphate dihydrate particles.Dibasic calcium phosphate dihydrate is also used in toothpasteand dentifrice formulations for its abrasive properties.

Description:

Dibasic calcium phosphate dihydrate is a white, odorless, tasteless powder or crystalline solid. It occurs as monoclinic crystals.

Stability and Storage Conditions

Dibasic calcium phosphate dihydrate is a nonhygroscopic, relatively stable material. However, under certain conditions the dihydrate can lose water of crystallization. This has implications for both storage of the bulk material and coating and packaging of tablets containing dibasic calcium phosphate dihydrate.The bulk material should be stored in a well-closedcontainer in a cool, dry place.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. The fine-milled grades can generate nuisance dusts and the use of a respirator or dust mask may be necessary.

6.10 Starch, Pregelatinized[126]

Nonproprietary Names

BP: Pregelatinised starch

PhEur: Amylum pregelificatum

USPNF: Pregelatinized starch

Synonyms

Compressible starch; Instastarch; Lycatab C; Lycatab PGS;Merigel;

Functional Category

Tablet and capsule diluent; tablet and capsule disintegrant;tablet binder.

Applications in Pharmaceutical Formulation or Technology

Pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, Diluent,and disintegrant.In comparison to starch, grades of pregelatinized starch may be produced with enhanced flow and compression characteristicssuch that the pregelatinized material may be used as atablet binder in dry-compression or direct compression processes.(4–14) In such processes, pregelatinized starch is self lubricating.However, when it is used with other excipients it may be necessary to add a lubricant to a formulation. Although magnesium stearate 0.25% w/w is commonly used for this purpose, concentrations greater than this may have adverse effects on tablet strength and dissolution. Therefore, stearic acid is generally the preferred lubricant with pregelatinized starch.Pregelatinized starch may also be used in wet granulation processes.

Description:

Pregelatinized starch occurs as a moderately coarse to fine,white to off-white colored powder. It is odorless and has a slight characteristic taste.Examination of fully pregelatinized starch as a slurry in cold water, under a polarizing microscope, reveals no significant ungelatinized granules, i.e., no 'maltese crosses' characteristic of the starch birefringence pattern. Examination of samples suspended in glycerin shows characteristic forms depending upon the method of drying used during manufacture: either irregular chunks from drum drying or thin plates. Partially pregelatinized starch (e.g., Starch 1500G and Sepistab ST200) show retention of birefringence patterns typical of unmodified starch granules.

Solubility: Practically insoluble in organic solvents. Slightly soluble to soluble in cold water, depending upon the degree of pregelatinization. Pastes can be prepared by sifting the pregelatinized starch into stirred, cold water. Cold-water soluble matter for partially pregelatinized starch is 10–20%.

Stability and Storage Conditions

Pregelatinized starch is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.

Materials and Methods

6. MATERIALS AND METHODS

Table 4 : Materials used in the study

Sl. No	Materials	Manufacturers/ suppliers
1	Amlodipine besylate	Arch Pharma labs
2	Losartan potassium	CPS Pharm labs
3	Microcrystalline Cellulose	RanQ Remedies, Mumbai.
4	Sodium Starch Glycolate	Dow Chemicals, Canada.
5	Starch	Vijaya Enterprises, Mumbai.
6	Crospovidone XL 10	Basf, Germany.
7	Pregelatinised starch	Vijaya Enterprises, Mumbai.
8	Ponceau 4 R Lake	Roha Dye Chem, Mumbai
9	Quinoline yellow lake	Roha Dye Chem, Mumbai
10	Methylene chloride	Gujarat Allealis & Chemicals
11	Colloidal silicon dioxide (Aerosil)	Cobot Sanmar, USA.
12	Instacoat	Dow Chemicals, Canada
13	Magnesium stearate	Amshi Drug and Chemicals, Gujarat.
14	Isopropyl alcohol	Lee Changyung Chemicals.

Table 5: Manufacturing Equipments used in the study

Sl. No	Equipments	Manufacturers/ Suppliers
1	Moisture balance	Sartorius, Germany
2	Vibratory sifter	Bectochem, Mumbai.
3	Planetary Mixer (vertical main drive)	Bectochem, Mumbai.
4	Hexagonal blender	Bectochem, Mumbai.
5	Rapid mixer Granulator	Bectochem, Mumbai.
6	Fluidized bed dryer	Bectochem, Mumbai.
7	Tray drier	Micro, S.B.Panchal and Co, India
8	Multi Mill	Bectochem, Mumbai.
9	Double Rotary Compression Machine (27 station)	Cadmach, India.
10	Dehumidifier	Tropical nortec, India
11	Vernier caliper	Mitutoyo corps, Japan
12	Blister Packing machine	Lab module, India
13	Photostability and humidity chamber	Thermolabs India Ltd.

Table 6: List of Instruments used in the study

Sl. No	Instruments	Manufacturers/ Suppliers
1	Electronic weighing balance	Shimadzu corporation, Japan
2	pH Meter	Mettler, Toledo, India.
3	Tap Density apparatus, ETD-1020	Electro lab, India.
4	Hardness tester	Monsanto , India
5	Friability Test Apparatus, ET-2	Electro lab, India.
6	Dissolution Apparatus, TDT-08L,	Electro lab, India.
7	Disintegration Apparatus	Electro lab, India.
8	FT-IR Spectrophotometer 8300	Shimadzu corporation, Japan
9	Differential scanning colorimetry	DSC Q2000 V24.4 build 114
10	UV- Visible Spectrophotometer (UV-1601)	Shimadzu corporation, Japan
11	HPLC with PDA detector	Waters HPLC, India.
12	Refrigerator	Whirlpool, India

Table 7: List of Reagents used in the study

Sl. No	Reagents/ chemicals	Manufacturers/suppliers
1	Potassium dihydrogen ortho phosphate AR	Rankem, New Delhi.
2	Sodium hydroxide AR	Rankem New Delhi.
3	Acetonitrile HPLC	Merck Canada.
4	Methanol HPLC	Merck, Canada.
5	Sodium dihydrogen ortho phosphate AR	Rankem, New Delhi.
6	Ortho phosphoric acid AR	Rankem, New Delhi.
7	Hydrochloric acid AR	Rankem, New Delhi
8	Whatman filter paper	Sartourious 292A, North America.
9	0.45 µ filter paper	Millipore, Canada.

6. METHODS

6.1 Preformulation studies

6.1.1 Physicochemical Interaction of drug and polymer:

Physicochemical Interaction of drug and excipients for amlodipine was done as per IP by the identification test carried out by the Fourier Transform Infra red spectrophotometer (FTIR) and the report was shown in figures 13-17.

Physicochemical Interaction of drug and excipients for losartan was done as per IP by the identification test carried out by the Fourier Transform Infra red spectrophotometer (FTIR) and the reports were shown in figures 13-17.

6.1.2 Calibration curve of Amlodipine Besylate:

100 mg of Amlodipine besylate was accurately weighed and dissolved in 25 ml of methanol in 100ml volumetric flask and the volume was made up to the mark using methanol, to make (1000 µg/ml) standard stock solution . Then 1 ml stock solution was taken in another 100 ml volumetric flask and further diluted in 100 ml of methanol to make (10 µg/ml) standard stock solution, then final concentrations were prepared with 0.1N HCL.The absorbance of standard solution was determined using UV/VIS spectrophotometer at 237nm.

6.1.3 Calibration Curve of Losartan Potassium

Accurately weighed 100mg Losartan Potassium was transferred into 100ml volumetric flask and dissolved in Small quantity of Methanol and the volume was made up with phosphate buffer pH 6.8 to give a stock solution of concentration of 1mg/ml. Further dilutions were made in the range of 2-20mcg/ml with phosphate buffer pH 6.8 and absorbance was measured at 235nm

6.2 Manufacturing process of Losartan Potassium and Amlodipine Besylate Bilayer Tablets:

6.2.1 Losartan Part:

- Sifting:

Sift the weighed quantities of Losartan Potassium, Microcrystalline cellulose plain , starch plain and Polyplasdone XL10 through Mesh 30#.

- Dry Mix and Granulation:

Transfer the sifted materials and Binder solution to Granulation area. Load the sifted material into the main bowl of rapid mixer and mix it for 15 minutes

- Initial Drying, Sifting and Milling:

Transfer the sifted materials into FBD main bowl. Dry the granules at 50 degrees Celsius. Sift the Semi-Dried granules through Mesh 20# and pass the retained granules through Multi-Mill fitted with 1.0 mm screen using knives forward medium speed.

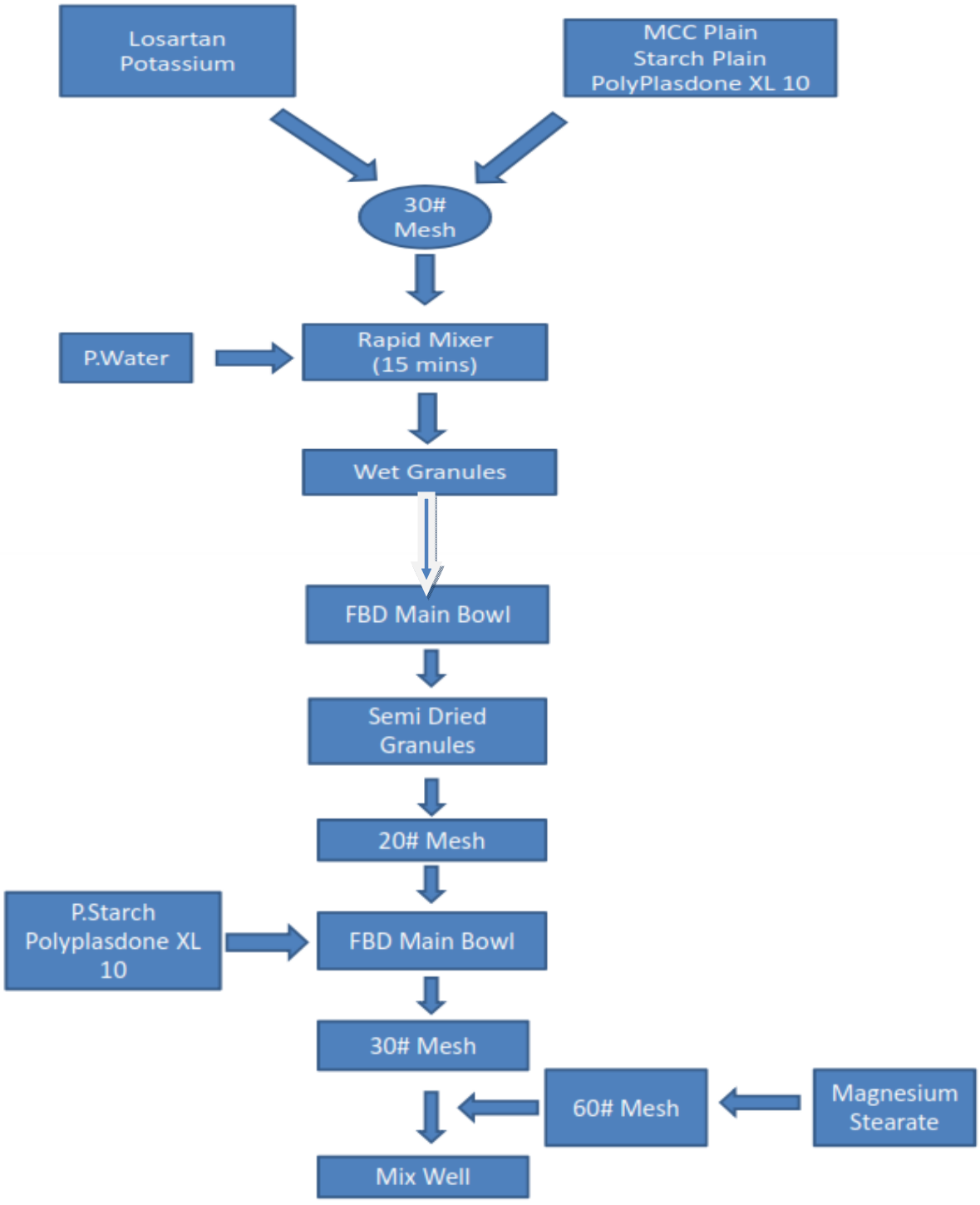
- Final drying and shifting:

Transfer the semidried sifted and milled granules into FBD bowl. Dry the semidried sifted granules at 50 degrees Celsius till the required LOD is achieved. Check the LOD of the granules (Limit: Between 2.0-4.0% w/w at 105 C)

- Lubrication:

Sift the following materials Pregelatinised Starch, and Polyplasdone XL10 through Mesh 30#.Load the sifted dried granules along with the above sifted materials into blender and blend it for 10 minutes. Finally sift Magnesium Stearate through Mesh 60#and mix for 5 minutes.

Figure 8: Flow chart of Losartan Potassium Granules preparation



6.2.2 Amlodipine Part:

- Sifting:

Sift the weighed quantities of Amlodipine Besylate , Dicalcium Phosphate Anhydrous , Microcrystalline cellulose pH 102, starch 1500, sodium starch glycolate,colloidal silicon dioxide and pass through Mesh30#. Ponceau 4R Lake was passed through Mesh100# and added to the above blend.

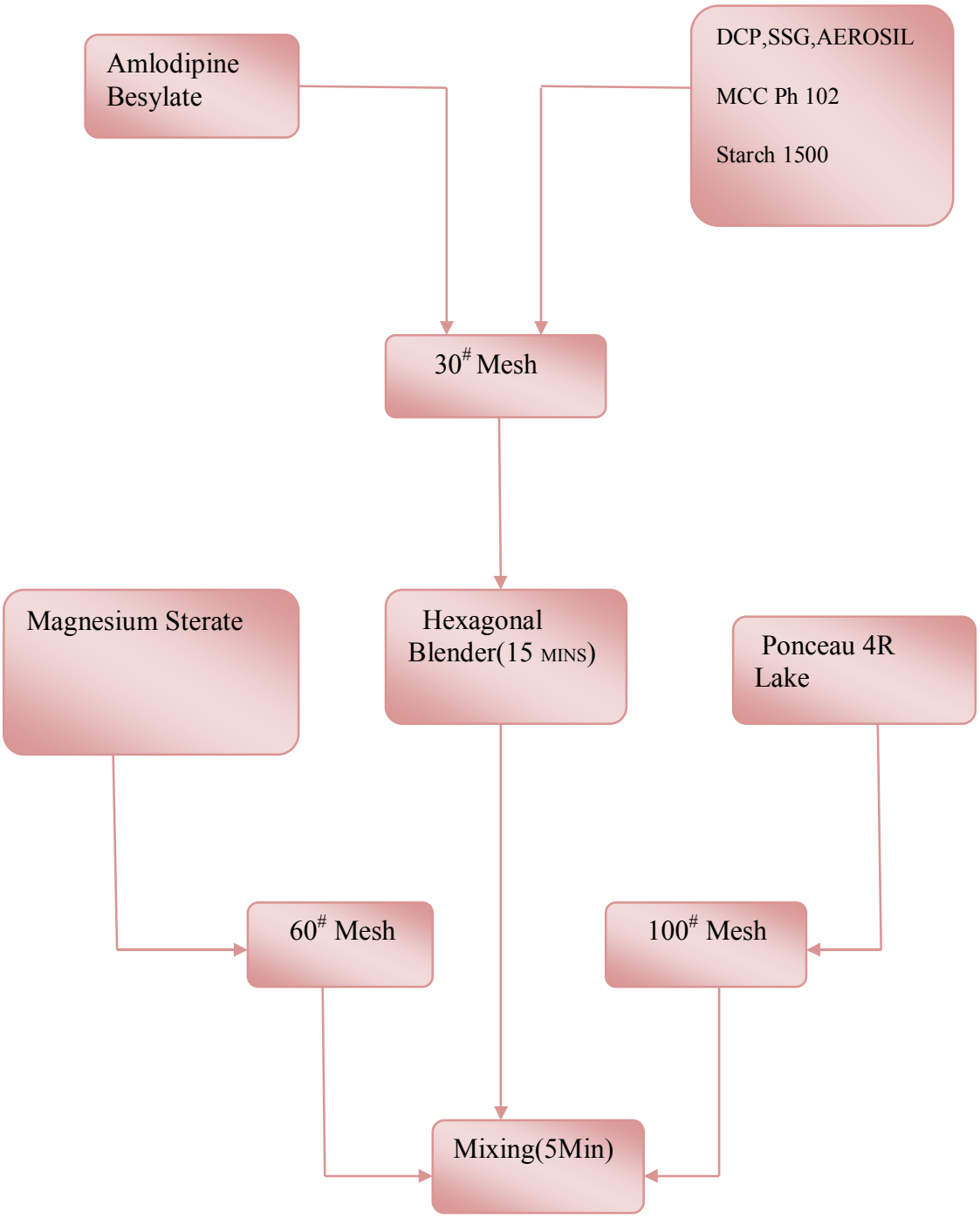
- Dry Mixing:

Load the sifted materials such as Amlodipine Besylate, Dicalcium Phosphate Anhydrous, Microcrystalline cellulose pH 102, Starch 1500, Sodium Starch glycolate, colloidal silicon dioxide and Ponceau 4R Lake in Hexagonal blender and mix for 15 minutes

- Lubrication:

Sift Magnesium Stearate through Mesh60# and add to the above mixture in the blender and mix for another 5 minutes.

Figure 9: Flow chart of Amlodipine Besylate Blend preparation:Direct Compression



6.2.3 Compression of Bilayer tablets

The quantity of granules for the immediate-release layer was compressed lightly using 27 stationary double rotary compression machine (Cad mach, India) using 13/32 inch circular standard plain punches. Over this compressed layer, required quantity of the other immediate release layer was placed and compressed to obtain hardness in the range of 8-12 kg/cm² to form a bilayer tablet of Immediate release of Losartan potassium and Immediate release of Amlodipine besylate. Then the compressed bilayer tablets were evaluated.

Figure 10: Flowchart of Bilayer Tablets of Amlodipine Besylate and Losartan Potassium Preparation

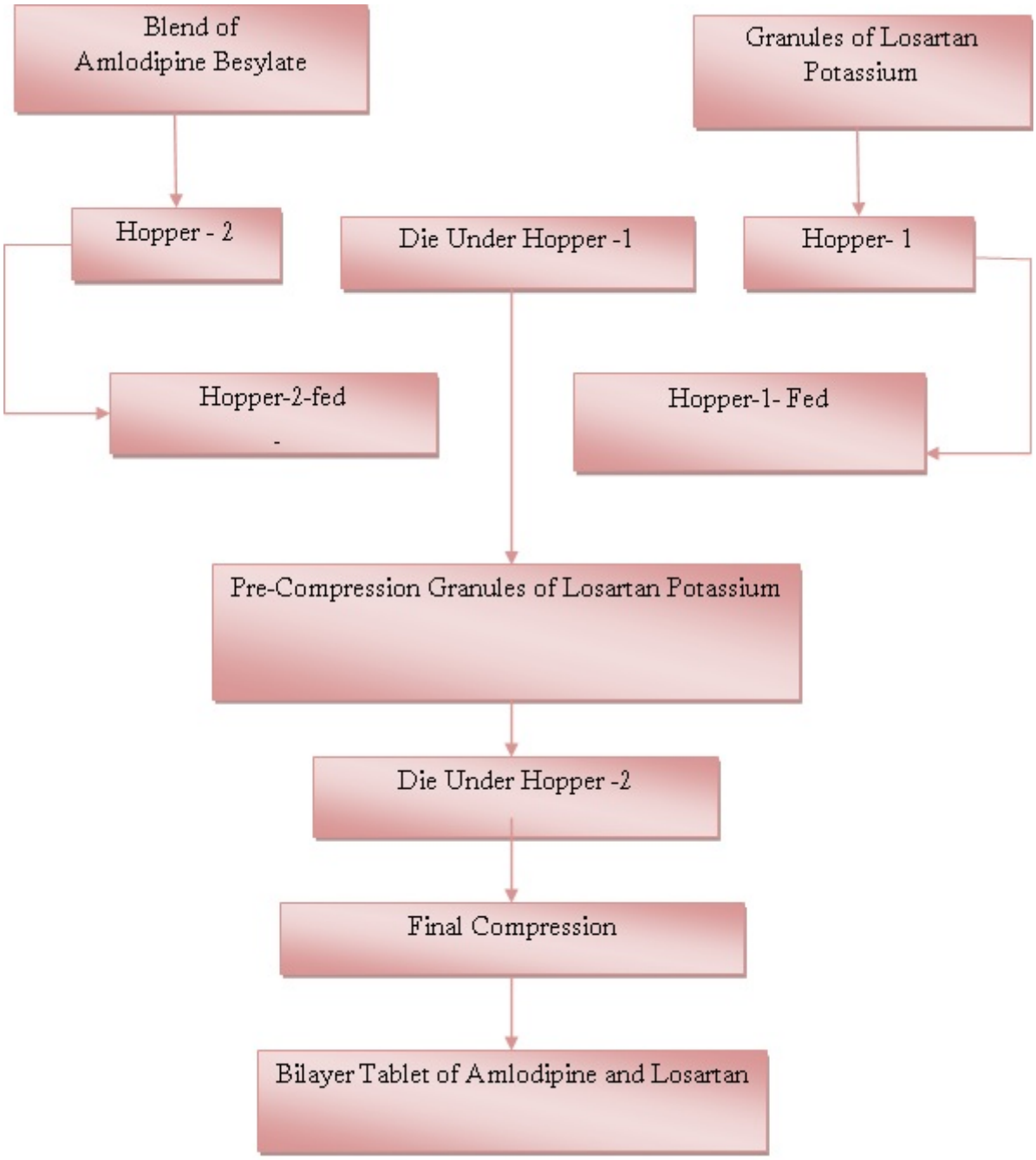


Table 8:Losartan Potassium Layer Trials

INGREDIENTS	L_1 (Mg/tab)	L_2 (Mg/tab)	L_3 (Mg/tab)	L_4 (Mg/tab)	L_5 (Mg/tab)	L_6 (Mg/tab)	L_7 (Mg/tab)	L_8 (Mg/tab)
Losartan Potassium	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00
MCC Plain	175.50	165.50	148.50	139.00	127.50	110.50	104.00	95.00
Starch Plain	-	10.00	10.00	15.00	15.00	25.00	25.00	30.00
Crospovidone XL 10	-	-	5.00	5.00	7.00	7.00	9.00	11.00
P.Water(For Granulation)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
LUBRICATION								
Pregelatinised starch	-	-	7.50	7.50	15.00	20.00	22.50	22.50
Crospovidone XL 10	-	-	4.50	9.00	11.00	13.00	15.00	17.00
Magnesium Stearate	4.50	4.50	4.50	4.50	4.50	4.50	4.50	4.50
Total Weight	230.00	230.00	230.00	230.00	230.00	230.00	230.00	230.00

Table 9: Amlodipine besylate layer trials

Ingredients	A1 (Mg/tab)	A2 (Mg/tab)	A3 (Mg/tab)	A4 (Mg/tab)	A5 (Mg/tab)	A6 (Mg/tab)
Amlodipine Besylate	7.00	7.00	7.00	7.00	7.00	7.00
DCP	45.00	43.00	43.00	42.00	42.00	40.00
MCC pH102	65.0	65.00	62.00	62.00	57.00	58.00
Pregelatinised Starch	-	2.00	4.00	4.00	8.00	8.00
SSG	-	-	1.00	2.00	3.00	4.00
Aerosil	1.00	1.00	1.00	1.00	1.00	1.00
Ponceau4R Lake	1.00	1.00	1.00	1.00	1.00	1.00
Magnesium Stearate	1.00	1.00	1.00	1.00	1.00	1.00
Total weight	120	120	120	120	120	120

Table 10: Formulation Trials of Bilayer tablets

Ingredients	F-1 (Mg/tab)	F-2 (Mg/tab)	F-3 (Mg/tab)	F-4 (Mg/tab)	F-5 (Mg/tab)	F-6 (Mg/tab)	F-7 (Mg/tab)	F-8 (Mg/tab)
Losartan Layer								
Losartan Potassium	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00
MCC Plain	175.50	165.50	148.50	139.00	127.50	110.50	104.00	95.00
Starch Plain	-	10.00	10.00	15.00	15.00	25.00	25.00	30.00
Crospovidone XL 10	-	-	5.00	5.00	7.00	7.00	9.00	11.00
P.Water(For Granulation)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
LUBRICATION								
Pregelatinised starch	-	-	7.50	7.50	15.00	20.00	22.50	22.50
Crospovidone XL 10	-	-	4.50	9.00	11.00	13.00	15.00	17.00
Magnesium Stearate	4.50	4.50	4.50	4.50	4.50	4.50	4.50	4.50
Amlodipine Layer								
Amlodipine Besylate	7.00	7.00	7.00	7.00	7.00	7.00	7.00	7.00
DCP	45.00	43.00	43.00	42.00	42.00	40.00	40.00	40.00
MCC pH102	65.0	65.00	62.00	62.00	57.00	58.00	58.00	58.00
Pregelatinised Starch	-	2.00	4.00	4.00	8.00	8.00	8.00	8.00
SSG	-	-	1.00	2.00	3.00	4.00	4.00	4.00
Aerosil	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ponceau 4R Lake	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Magnesium Stearate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Total weight	350	350	350	350	350	350	350	350

6.3 Evaluation of Granules.

6.3.1 Bulk density [127]:

Bulk density is the ratio of the weight of the powder to the bulk volume it occupies. it is expressed in gm/ml. A weighed quantity of powder blend previously shaken to break any agglomerates formed, was introduced in to a measuring cylinder and the volume was noted.

Bulk density was calculated using the following equation;

$$\text{Bulk density} = \frac{\text{Mass of the powder Blend taken}}{\text{Volume occupied by the powder blend}}$$

6.3.2 Tapped density[127]:

A weighed quantity of powder blend previously shaken to break any agglomerates formed, was introduced in to a measuring cylinder and the volume was noted. The cylinder was placed in the tapped density apparatus and allowed to fall under its own weight on to a hard surface (USP-II), that provides fixed a drop of 3mm(±10%) at a nominal rate of 250 drops per minute is used. Tapping was continued until no further change in volume was noted. Td was calculated using the following equation;

$$\text{Tapped density} = \frac{\text{Mass of the powder Blend taken}}{\text{Tapped Volume of the powder blend}}$$

6.3.3 Carr's Index[127]:

Carrs Index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20 is defined as the free flowing material.[48] The formula for

Carrs Index is as below:

$$\text{Carrs Index (\%)} = 100 \left\{ 1 - \frac{Bd}{Td} \right\}$$

Table 11: Carr's index values and type of flow

Carr's index	Type of flow
5-15	Excellent
12-15	Good
18-21	Fair
23-30	Poor
33-38	Very poor
>40	Extremely poor

6.3.4 Hausner's ratio[127]:

It indicates the flow properties of the powder and is measured by the ratio of tapped

density to the bulk density

Hausners ratio = (Tapped density)/ (Bulk density)

Table 12: Hausners ratio and flow characters

Flow characters	Hausner ratio
Excellent	1.11
Good	1.12 – 1.18
Fair	1.19 – 1.25
Passable	1.26 – 1.34

Poor	1.35 – 1.45
Very poor	1.46 – 1.59
Very Very poor	>1.60

6.3.5 Angle of repose[127]:

Angle of Repose is an indication of the frictional forces existing between granule particles. The maximum angle possible between the surface of the pile of granules and the horizontal plane gives the angle of repose:

$$\tan \theta = h / r$$

Where, θ is the angle of repose; h is the height of the heap of powder and r is the radius of the heap of the powder. Therefore $\theta = \tan^{-1} (h/r)$.

Method: Weighed quantity of granules were poured through the funnel from the fixed height on the graph paper. Then circumference of the heap was marked by pencil. The radius of the circle formed was measured and angle of repose then calculated on the parameter found out from the radius of circle and height of the heap.

Table 13: Angle of repose values and type of flow

Angle of repose(θ)	Type of flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

6.3.6 Moisture content:

Initially 5 g of weighed granules were taken and kept for drying at 105^0 C for a required time in a oven. Then removed and again reweighed and noted as final weight. The difference in weight was noted as moisture content.

$$\text{Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

6.4 EVALUATION OF TABLETS:

6.4.1 Evaluation of physical characteristics

The formulated tablets were evaluated for the following physical parameters,

6.4.2 Thickness:

Thickness depends on die filling, physical properties of material to be compressed. There is possibility of small variation in the thickness of individual tablet in a batch. But it should not be apparent to the unaided eye. The thickness and diameter can be measured by vernier calipers.

6.4.3 Hardness:

Tablet must possess sufficient strength or hardness and can be measured by Monsanto hardness tester. Ten tablets were randomly picked from each formulation and were evaluated for hardness and can be expressed in Kg/cm^2.

6.4.4 Friability:

Friability can be performed in Roche friabilator, Preweighed ten tablets were introduced in the friabilator. Then the machine was operated for 100 revolutions. Tablets were dropping from a distance of six inches with each revolution. Tablets were then dusted and reweighed. Loss of less than 1% in weight is considered to be within the specifications and acceptable.

$$F\ (\%) = \frac{\text{Initial wt.} - \text{Final wt.}}{\text{Initial wt.}} \times 100$$

6.4.5 Weight variation test[128]:

Twenty tablets were selected randomly and weighed individually. Calculate average weight and compare the individual tablet weight to the average. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in table and none deviate by more than twice the percentage.

Table 14: IP Specifications for weight variation

Average weight of tablet (mg)	Percentage difference allowed
80 mg or less	10
More than 80 mg but less that 250 mg	7.5
250 mg or more	5

6.4.6 Disintegration Time[128]

The in-vitro disintegration time was determined by using disintegration test

apparatus. One tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass in the apparatus was measured in seconds.

6.4.7 Drug content:Assay: (BY HPLC)

For Amlodipine Besylate and Losartan Potassium

Procedure:

Chromatographic System

Column : Inertsil ODS C8 25×4.9mm

Column temperature : Ambient

Flow rate : 1.0 ml / minute

Injection volume : 20 µl.

Detector Wave length : 237 nm

Run Time : 25 minutes.

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Diluent : Buffer:Methanol:ACN(55:18:12).

Instrument set up : isocratic

Type of detector : UV

Buffer

Dissolve 0.68g of potassium di hydrogen phosphate in 1000 ml of water,add 4ml of tryethylamine and adjust the pH to 5.0 with OPA

Mobile Phase preparation:

Mix 850 ml of buffer, 75 ml of methanol and 75 ml of acetonitrile

Standard Preparation

Weigh accurately 40mg of Amlodipine from amlodipine besylate working standard and transfer into a 100 ml volumetric flask, dissolve and dilute to volume with mobile phase(Solution A) .40mg of losartan potassium was weighed transferred into standard volumetric flask and 10ml of solution A was added and the volume was made up with the mobile phase

Sample Preparation

10 tablets were randomly selected from collected samples of analysis, Powdered and transferred into 250ml standard flask. 170ml of mobile phase was added in the flask, dissolved and sonicated for 30mins and diluted to the volume with the mobile phase. 5ml of the above solution was transferred to 25ml standard flask and volume was made to 25ml.

Procedure

Inject 20 µL portion of diluent as blank ,6 replicate injections of standard preparation and one injection of each test preparation into the HPLC system ,record the chromatograms and measure the peaks response.

Calculation:

For Amlodipine Besylate

$$= \frac{\text{Spl Area}}{\text{Std Area}} \times \frac{\text{Std. wt}}{100} \times \frac{10}{100} \times \frac{250}{\text{Spl wt}} \times \frac{25}{5} \times \frac{\text{Purity}}{100} \times \frac{\text{Avg wt}}{1} \times \frac{\{100\text{-LOD}\}}{100} \times \text{C.F}$$

For Losartan Potassium

Spl Area Std. wt 100 25 Avg wt Purity {100-LOD}

$$= \frac{}{\text{Std Area}} \times \frac{100}{\text{Spl wt}} \times \frac{5}{1} \times \frac{100}{100}$$

6.4.8 *In vitro* Dissolution studies:

Procedure of Dissolution of bilayer tablets:

Six tablets of Amlodipine Besylate and Losartan Potassium (Bilayer tablets) were introduced in the dissolution apparatus USP Type II (paddle). The medium used was 900 ml of 0.01 M sodium acetate buffer, pH 4.5 maintained with glacial acetic acid and the dissolution mediums were maintained at the temperature of 37.5± 0.5^0 C, the RPM was set at 75. The Dissolution was carried out for 30 minutes and sample withdrawn at predetermined

intervals . The estimation was carried out by HPLC method. The optimized formulation was compared with the market product.

Estimation of Amlodipine by HPLC:

Chromatographic system:

Apparatus	: HPLC, PDA Detector
Column	: Inertsil ODS C8, 250× 4.6 mm
Wave length	: 237 nm
Injection volume	: 50 µl
Flow rate	: 1.0 ml/min
Column Temperature	: Ambient
Diluent	: Dissolution medium
Mobile phase	: Buffer:Methanol:ACN (55:18:22)
Retention time	: 15 minutes
Instrument set up	: Isocratic

Standard preparation:

Accurately 75.3mg of Amlodipine besylate was taken in 100ml of volumetric flask and 25ml of diluents were added and sonicated to dissolve and the volume was made up with diluents to 100ml. From this 10ml was pipetted out in to 100ml volumetric flask and volume was made with a diluents. From the above solution another 10 ml withdrawn and made upto 100 ml and Filtered through 0.45 micron membrane filter.

Sample preparation:

The dissolution parameters were set and one tablet is placed in each basket and care was taken to exclude air bubbles from the surface of the tablets and immediately the apparatus was started, 10ml of the sample was withdrawn and filter through whatmann filter paper, 10ml of solution was replaced in to dissolution medium, the same procedure was repeated at other time intervals.

Procedure:

50 micro liters of filtered portion of the standard and sample solution was injected in to HPLC system. The chromatogram was recorded and responses were measured for major peaks. The % release of Amlodipine besylate was calculated by using following expression.

Calculation for Amlodipine Besylate:

$$= \frac{\text{Spl Area}}{\text{Std Area}} \times \frac{\text{Std. wt}}{100} \times \frac{10}{100} \times \frac{10}{100} \times \frac{900}{1} \times \frac{100}{\text{LC}} \times \frac{\text{Purity}}{100} \times \frac{100\text{-LOD}}{100} \times \text{Conversion Factor}$$

Conversion Factor:

Molecular weight of Amlodipine besylate =567.10

Molecular weight of Amlodipine =410.10

Conversion factor to convert amlodipine besylate to amlodipine(pure)= $\frac{410.10}{567.10} = 0.721$

Estimation of Losartan by HPLC:

Chromatographic system:

Apparatus : HPLC, PDA Detector

Column	: Inertsil ODS C8, 250× 4.6 mm, 5µ
Wave length	: 237 nm
Injection volume	: 50 µl
Flow rate	: 1.0 ml/min
Column Temperature	: Ambient
Diluents	: Acetonitrile and Dissolution medium
Mobile phase	: Buffer:Methanol:ACN (55:18:22)

Standard preparation:

Accurately weighed 56.9mg of Losartan Potassium was taken in 100ml volumetric flask and 50ml of diluents and volume was made up by the diluents to 100ml. From this 10ml was pipetted out in to 100ml volumetric flask and volume was made up with dissolution medium.

Sample preparation

The dissolution parameters were set and one tablet was placed in to each basket care was taken to exclude air bubbles from the surface of the tablets and immediately the apparatus was started, 10ml of the sample was withdrawn and filter through whatmann filter paper, 10ml of solution was replaced in to dissolution medium, the same procedure was repeated at other time intervals.

Procedure

50 micro liters of filtered portion of the standard and sample solution was injected in to HPLC system. The chromatogram was recorded and the responses were measured for the major peaks. The % release of Losartan Potassium was calculated an calculated and followed by the expression.

Calculation for Losartan Potassium

$$= \frac{\text{Spl Area}}{\text{Std Area}} \times \frac{\text{Std. wt}}{100} \times \frac{10}{100} \times \frac{900}{1} \times \frac{100}{\text{LC}} \times \frac{\text{Purity}}{100} \times \frac{100\text{-LOD}}{100}$$

6.5 Coating of bilayered tablets:

Table 15: Coating solution composition:

Ingredients	Quantity for 1000 tablets in grams
Insta coat	10.5
Quinoline yellow lake	0.75
Iso propyl alcohol	117.50
Methylene chloride	97.94

Instacoat: percentage of solution-5.25% w/w

6.5.1Film coating solution preparation:

Isopropyl alcohol was transferred into a clean stainless steel vessel. Instacoat (IC-S-10) was

added to the part of isopropyl alcohol. To the another part of isopropyl alcohol, quinoline yellow lake was added and was passed through the colloidal mill and mixed with the above solution. Finally methylene chloride was added to the above solution with continuous stirring. Care was taken that there were no lumps formation in the solution visually. The above solution was filtered through mesh 100# nylon cloth. The above solution was transferred into a SS vessel of pressure vessel fitted with stirrer.

Table 16: Coating process specifications:

S.No	Parameters	Limits
1.	Pan speed	4 to 5 rpm
2.	Temperature	
	Inlet	45 c
	Outlet	40 c(±2 c)
3.	Gun operating pressure	NLT 4kg/cm2
4.	Atomizing air pressure	3 – 4.5 kg/cm2
5.	Spray rate	100-150ml/min
6.	Drying time	

Table 17: Specifications of coating solution:

S.No	Parameters	Limits
1.	Uniformity of colour	NA
2.	Viscosity	600-700cps
3.	Weight gain	3%
4.	Percent solid content	5%w/v
5.	Microbial load	NA

Table 18: Coating tablet specifications:

S.No	Parameters	Limits
1.	Description	Yellow colour, circular shaped,plain surface film coating tablet
2.	Theoretical average weight	360mg±3%
3.	Uniformity of weight	360mg±5%
4.	Thickness	4.25-4.30mm
5.	Disintegration time	NMT 30 minutes

6.6 Stability Studies[129].

The stability studies were carried out according to ICH to assess the drug formulation stability. Optimized F8 formulation was sealed in aluminium packaging laminated with polyethylene. Sample were kept at 40°C and 75% RH for 1,2,3,6 months. At the end of the study period, the formulation was observed for change in physical appearance, color, drug content and drug release characteristics. The values were showed in the Table No.37.

Results

7. Results

7.1 Calibration Curves

Table 19: Calibration Curve of Amlodipine Besylate

Calibration Curve of Amlodipine Besylate		
S.NO	Concentration(mcg/ml)	Absorbance
1	2	0.072
2	4	0.149
3	6	0.211
4	8	0.270
5	10	0.346
6	12	0.410
7	14	0.466
8	16	0.523
9	18	0.597
10	20	0.647

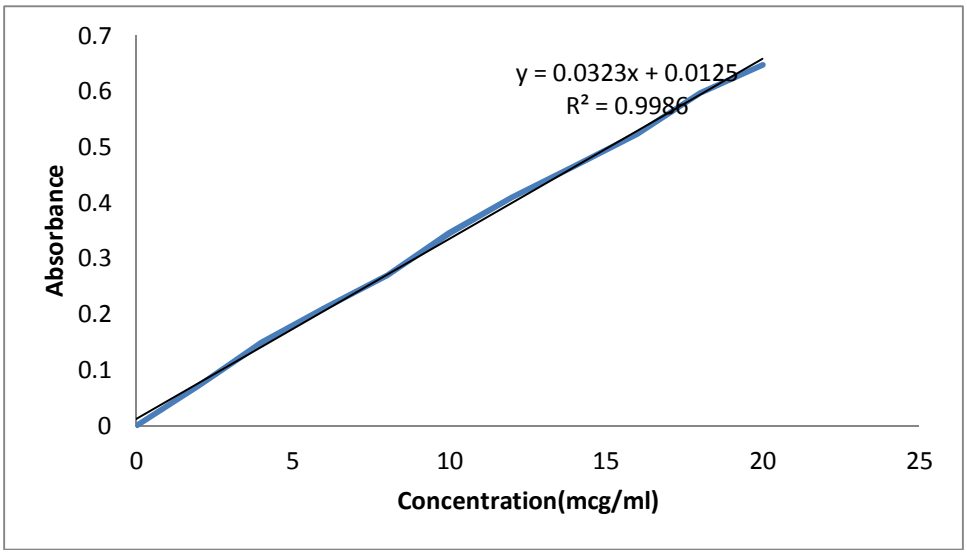


Figure 11: Calibration Curve of Amlodipine Besylate

Table 20: Calibration Curve of Losartan Potassium

Calibration Curve of Losartan Potassium		
S.NO	Concentration (Mcg/ml)	Absorbance
1.	2	0.122
2.	4	0.209
3.	6	0.341
4.	8	0.483
5.	10	0.555
6.	12	0.625
7.	14	0.751
8.	16	0.814
9.	18	0.888
10.	20	0.960

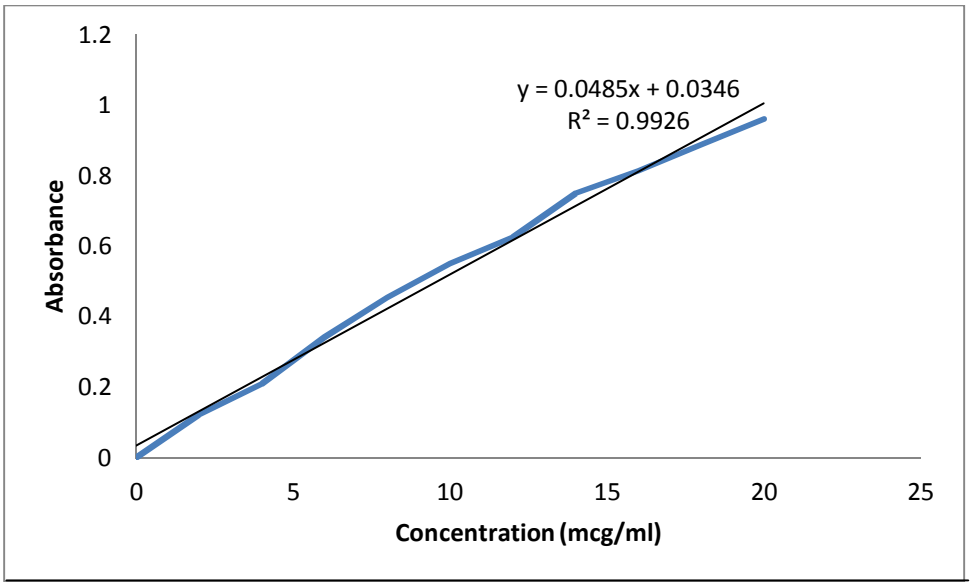


Figure 12:Calibration Curve of Losartan Potassium

7.2 Preformulation Studies:

Physicochemical Interaction of drug and excipients:

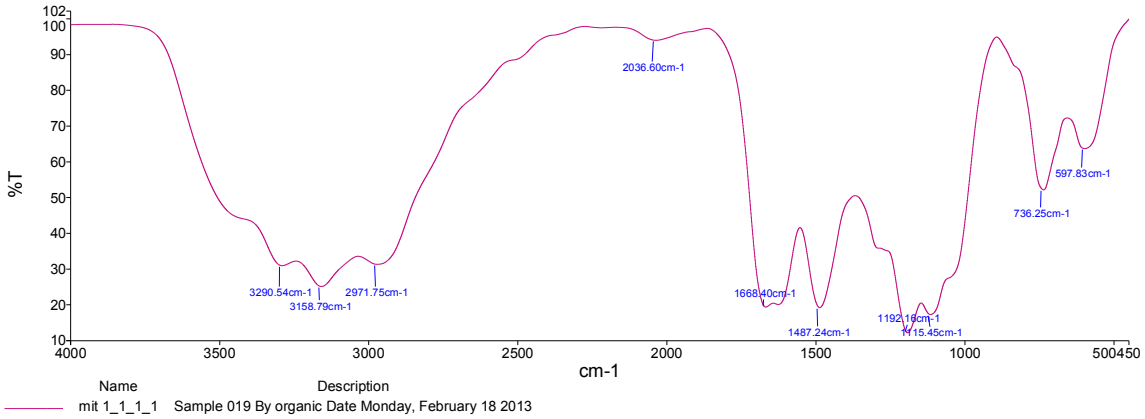


Figure 13: IR spectra of Amlodipine Besylate (pure drug)

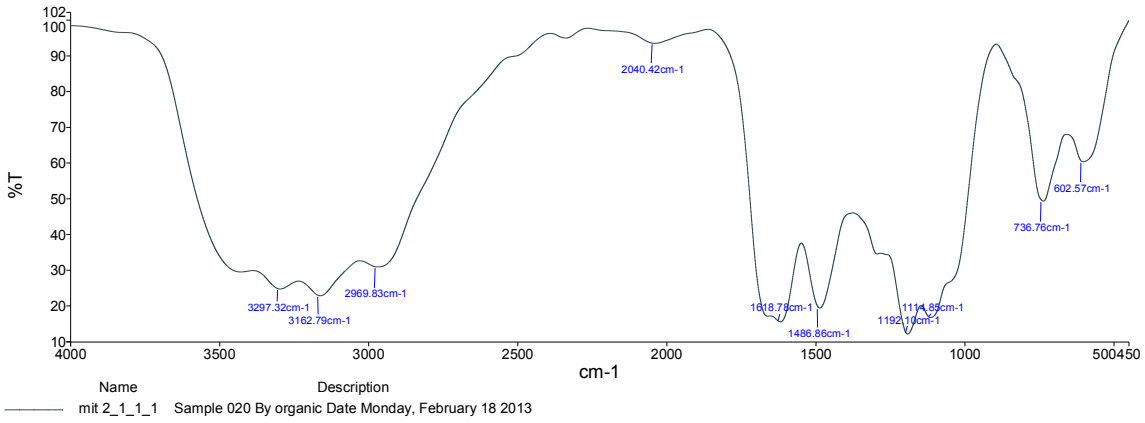


Figure 14: IR Spectra of Losartan Potassium(Pure drug)

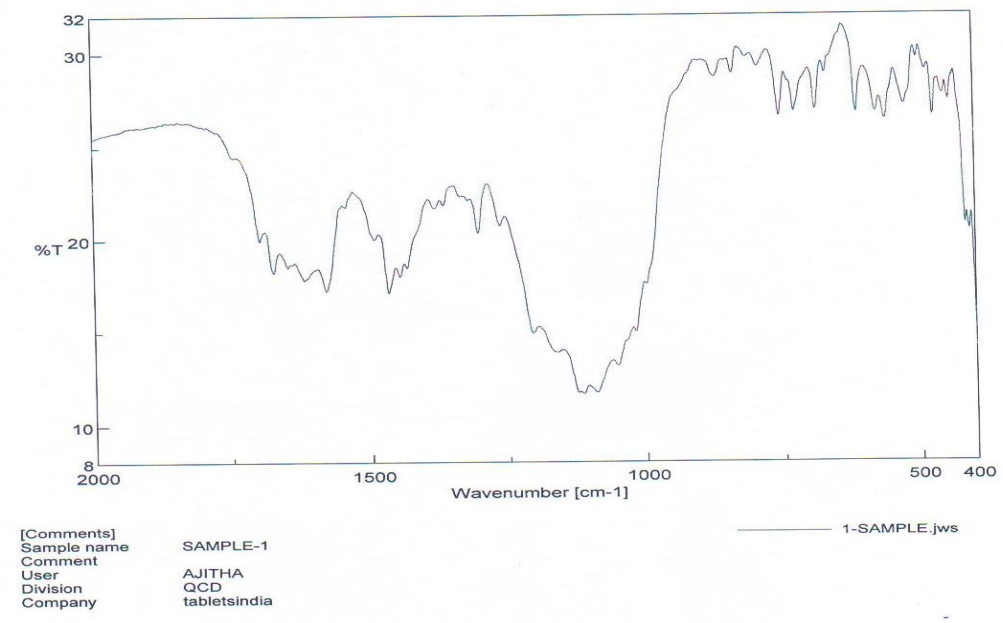


Figure 15: IR spectra of Optimized Amlodipine Besylate Layer (A6)

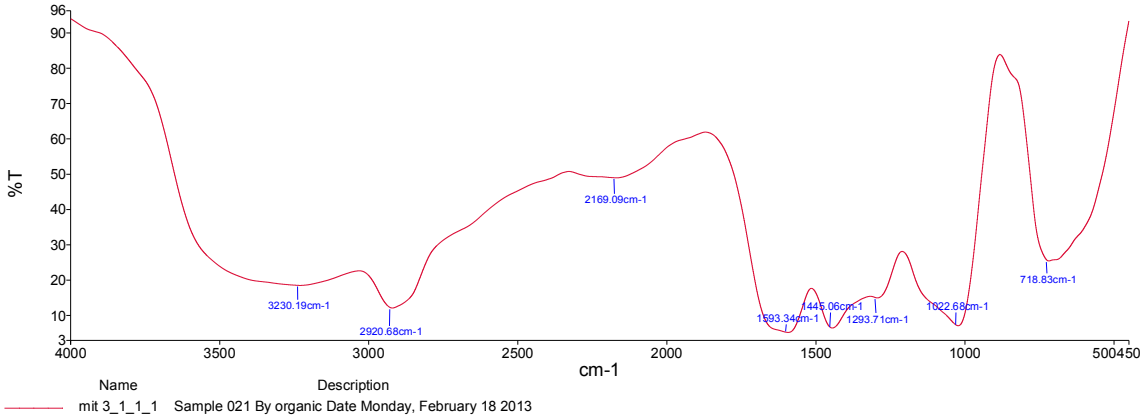


Figure 16: IR Spectra of Optimized Losartan Potassium Layer(L8)

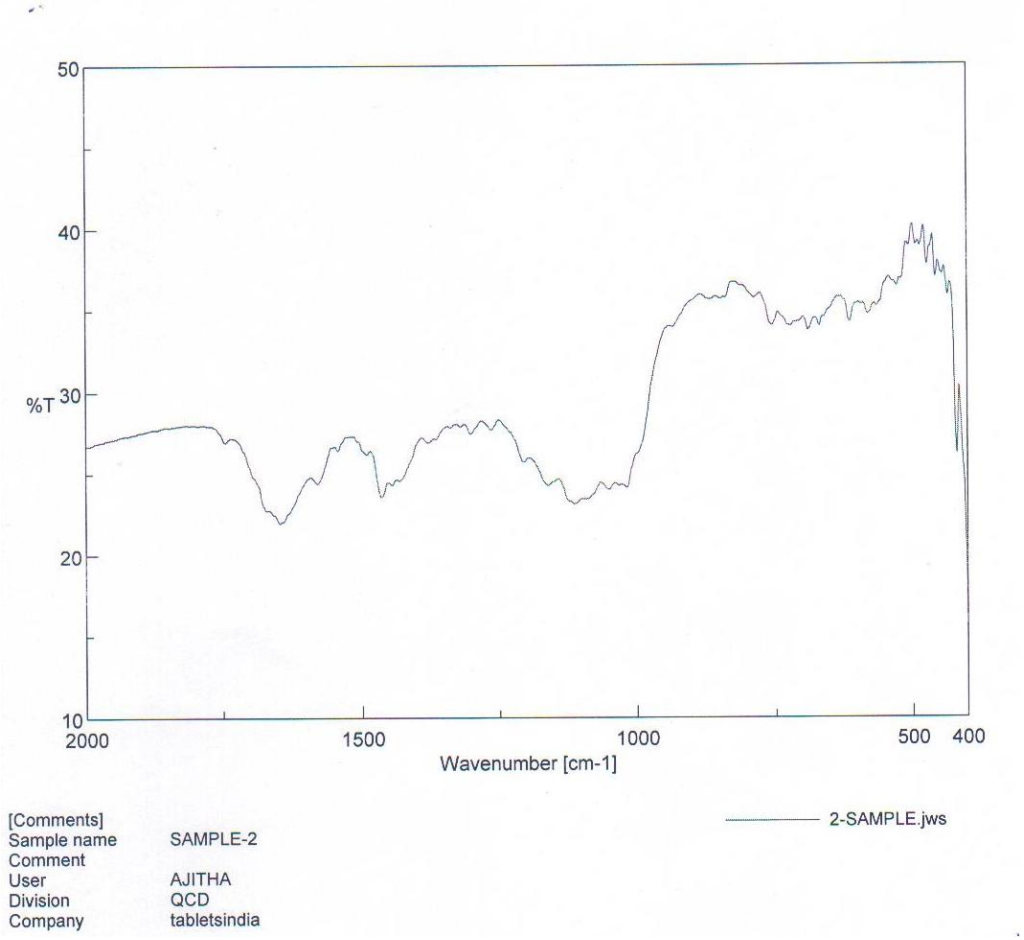


Figure 17: IR spectra of Optimized Coated Bilayer Formulation

Table 21:IR Interpretations for Pure drug

S.No	Functional groups	Characteristic peaks cm^{-1}	Observed peaks cm^{-1} Amlodipine	Observed peaks cm^{-1} Losartan
1	OH	3100	-	3162.79
2	N-H	3500-3100	3230.19	-
3	C=0	1740	1687.41	1665.69
4	Aromatic C-H	3100	2971.75	3162.43
5	C-0	1300-1100	1116.92	-

7.3 Precompression parameters:

Table 22:Precompression parameters for Amlodipine layer blend

FORMULATION	BULK DENSITY **(g/ml)**	TAPPED DENSITY **(g/ml)**	HAUSNER'S RATIO	CARR'S INDEX (%)	ANGLE OF REPOSE **(θ)**
A1	0.634±0.002	0.740±0.001	1.16±0.01	14.32±0.65	26.3º±0.98
A2	0.623±0.001	0.754±0.003	1.21±0.01	17.37±0.87	29.8 º±1.17
A3	0.578±0.002	0.722±0.004	1.25±0.03	19.94±1.11	28.8 º±0.75
A4	0.595±0.004	0.758±0.002	1.27±0.01	21.20±0.87	28.6 º±0.88
A5	0.589±0.001	0.737±0.002	1.25±0.02	20.08±0.45	28.4 º±1.24
A6	0.613±0.003	0.766±0.003	1.24±0.02	19.73±0.72	29.4 º±1.32

Table 23:Precompression parameters for Losartan layer blend

FORMULATION	BULK DENSITY (g/ml)	TAPPED DENSITY (g/ml)	HAUSNER'S RATIO	CARR'S INDEX (%)	ANGLE OF REPOSE (θ)	MOISTURE CONTENT (%)
L1	0.488±0.002	0.605±0.002	1.17±0.01	19.39±0.89	30.4 º±1.40	4.3±0.2
L2	0.479±0.003	0.604±0.006	1.25±0.01	20.60±1.12	31.7 º±1.23	4.4±0.2
L3	0.491±0.001	0.617±0.001	1.26±0.03	20.89±1.45	32.5 º±0.95	4.5±0.1
L4	0.487±0.002	0.612±0.002	1.25±0.01	20.41±1.23	31.8 º±0.89	4.2±0.2
L5	0.490±0.007	0.599±0.002	1.09±0.02	18.19±1.16	26.2 º±1.15	4.5±0.1
L6	0.479±0.008	0.605±0.001	1.26±0.01	20.82±1.31	29.9 º±1.63	4.1±0.2
L7	0.486±0.009	0.609±0.003	1.25±0.02	20.32±0.93	29.4 º±1.34	4.3±0.1
L8	0.477±0.005	0.600±0.004	1.25±0.02	20.51±0.96	30.3 º±0.90	4.2±0.1

7.4 Post compression parameters:

Table 24 :Post compression parameters for core bilayer tablets.

BATCH	THICKNESS (mm)	HARDNESS (kg/cm^2)	FRIABILITY %	DISENTEGRATION TIME(MINUTES)
F-1	4.09±0.011	6.4±0.57	0.22	11m 53s
F-2	4.21±0.015	7.3±0.73	0.19	9m 14s
F-3	4.32±0.014	7.8±0.34	0.13	7m 40s
F-4	4.28±0.012	8.9±0.69	0.09	7m 47s
F-5	4.24±0.011	8.5±0.76	0.15	6m 18s
F-6	4.35±0.010	6.4±0.43	0.22	6m 41s
F-7	4.26±0.011	7.9±0.67	0.18	6m 25s
F-8	4.19±0.013	8.8±0.82	0.17	5m 30s

Table 25: Post compression parameters for coated tablets.

BATCH	THICKNESS (mm)	DISENTEGRATION TIME(Minutes)	ASSAY %
F-1	4.21±0.011	10m 35s	(A)-92.32
			(L)-97.34
F-2	4.30±0.012	10m 28s	(A)-91.66
			(L)-98.15
F-3	4.43±0.015	8m 57s	(A)-90.78
			(L)-97.56
F-4	4.39±0.014	8m 42s	(A)-94.98
			(L)-96.87
F-5	4.34±0.017	7m 25s	(A)-93.71
			(L)-97.87
F-6	4.46±0.012	7m 32s	(A)-92.45
			(L)-94.79
F-7	4.37±0.011	6m 44s	(A)-94.06
			(L)-95.50
F-8	4.31±0.014	6m 45s	(A)-94.70
			(L)-96.87

Table 26: Weight Variation Test

BATCH	F1	F2	F3	F4	F5	F6	F7	F8
AVG WT (20 TAB)	362±0.71	371±0.84	364±0.71	369±0.78	358±0.63	365±0.82	370±0.68	363±0.69
% max positive deviation	+1.98	+3.23	+2.76	+1.98	+2.41	+3.14	+2.23	+2.65
% min negative deviation	-1.34	-2.75	-1.87	-2.75	-2.63	-2.25	-1.87	-1.98

Model Chromatograms:

Figure 18:Assay Diluent

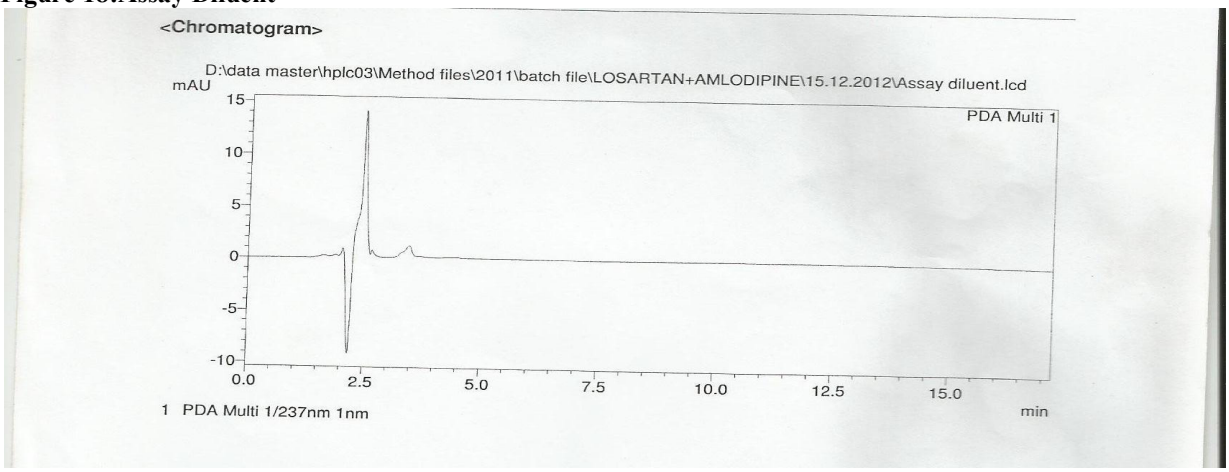


Figure 19:Assay Sample

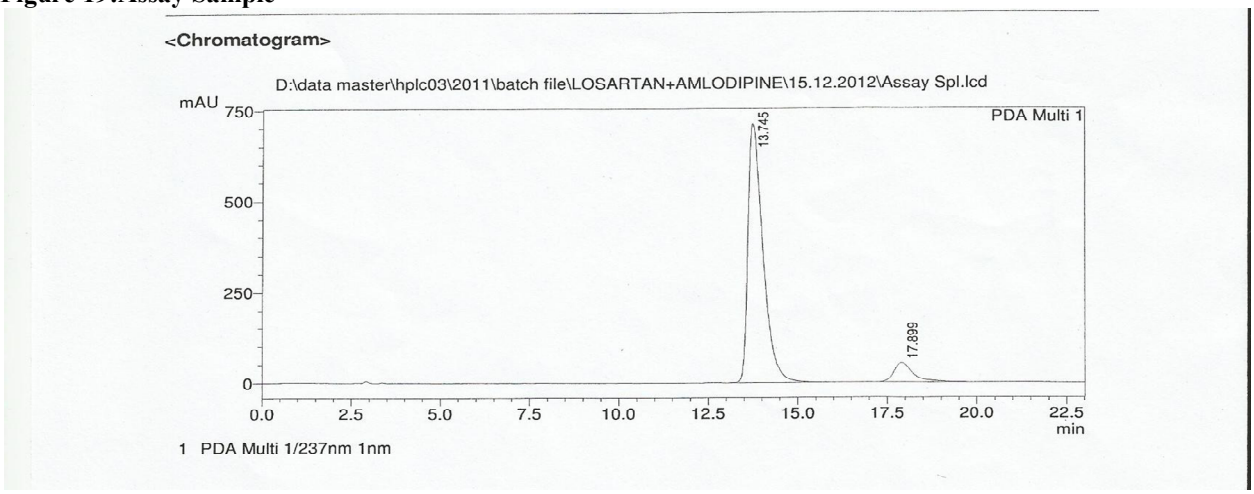
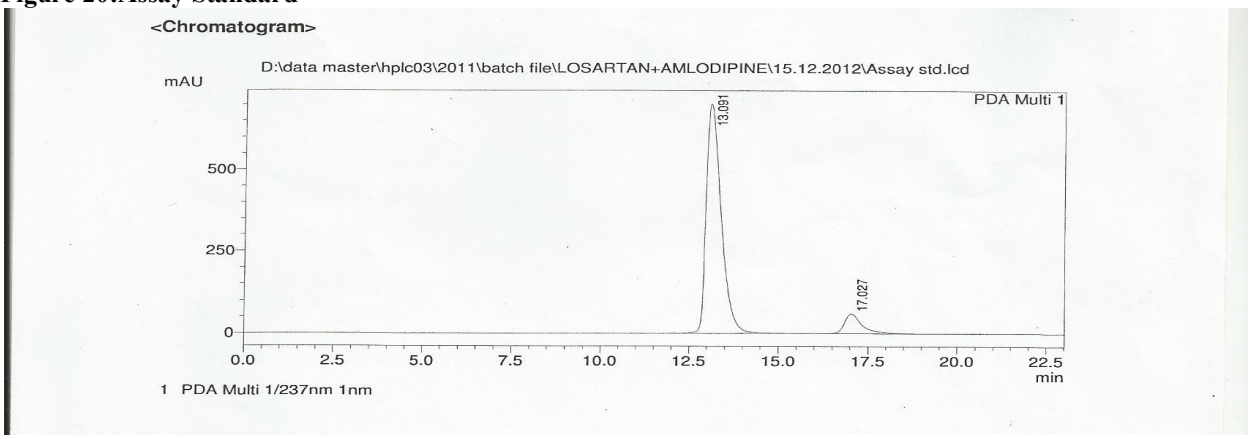


Figure 20:Assay Standard



7.5 *In vitro* dissolution studies

***Table 27 : In vitro dissolution profile of Bilayer tablet* F-1**

Immediate Release Layer of Amlodipine Besylate			
S.NO	Time (mins)	Amount of drug release (mg)	Cumulative Drug release (%)
1.	5	1.15±0.08	24.63
2.	10	1.98±0.13	42.40
3.	15	2.43±0.19	52.13
4.	20	2.86±0.24	61.36
5.	25	3.22±0.16	68.67
6.	30	3.46±0.21	73.62
Immediate Release Layer of Losartan Potassium			
S.NO	Time (mins)	Amount of drug release (mg)	Cumulative Drug release (%)
1.	5	10.24±0.21	21.12
2.	10	17.67±0.43	36.54
3.	15	24.01±0.24	49.60
4.	20	27.42±0.36	56.65
5.	25	30.41±0.87	62.81
6.	30	33.12±0.67	68.40

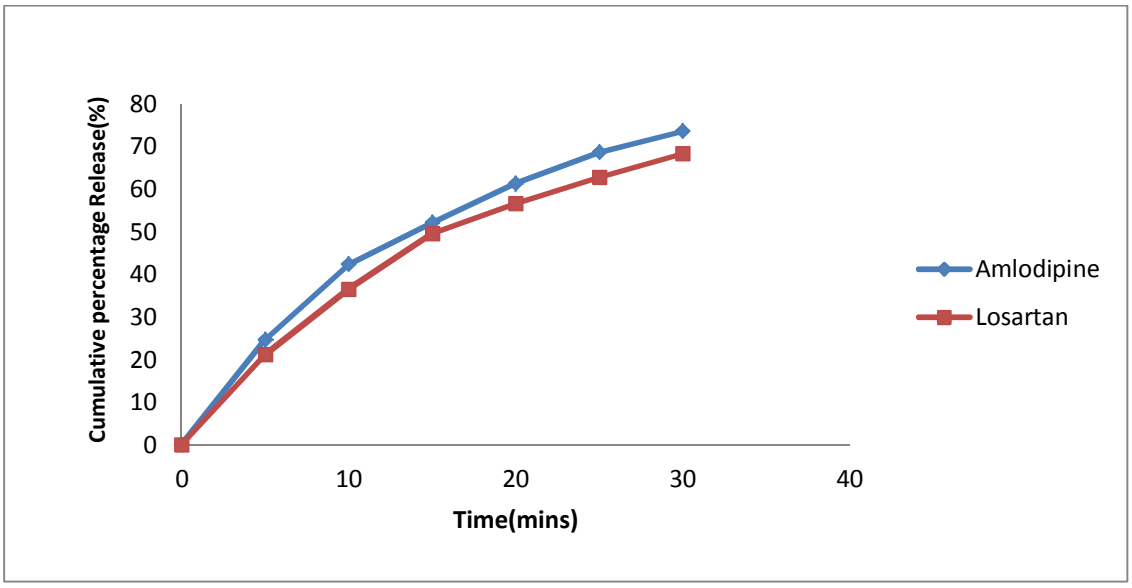


Figure 21: *In vitro* Dissolution Profile of Formulation F-1

Table 28:*In vitro dissolution profile of Bilayer tablet* F-2

Immediate Release Layer of Amlodipine Besylate			
S.NO	Time (mins)	Amount of drug release (mg)	Cumulative Drug release (%)
1.	5	1.85±0.14	39.50
2.	10	2.51±0.11	53.73
3.	15	2.80±0.23	59.98
4.	20	3.16±0.19	67.78
5.	25	3.42±0.12	73.31
6.	30	3.57±0.15	76.15
Immediate Release Layer of Losartan Potassium			
S.NO	Time (mins)	Amount of drug release (mg)	Cumulative Drug release (%)
1.	5	12.78±0.24	26.36
2.	10	19.34±0.33	39.93
3.	15	28.15±0.28	58.12
4.	20	31.35±0.56	64.73
5.	25	33.85±0.75	69.88
6.	30	34.99±0.56	72.25

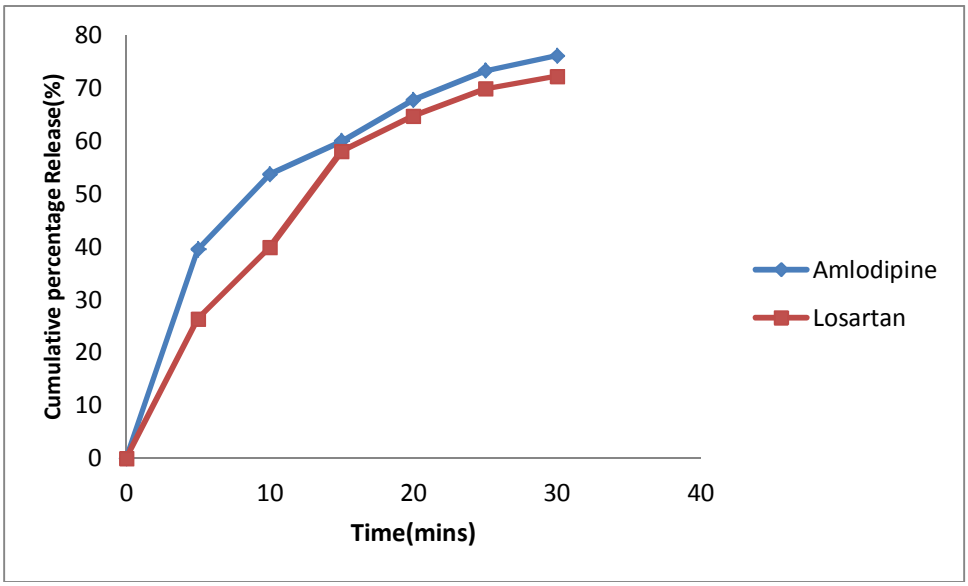


Figure 22: *In vitro* Dissolution Profile of Formulation F-2

Table 29: ***In vitro dissolution profile of Bilayer tablet*** **F-3**

Immediate Release Layer of Amlodipine Besylate			
S.NO	Time (mins)	Amount of drug release (mg)	Cumulative Drug release (%)
1.	5	2.37±0.16	50.60
2.	10	2.68±0.10	57.42
3.	15	2.99±0.21	64.54
4.	20	3.21±0.11	68.91
5.	25	3.46±0.15	74.23
6.	30	3.71±0.19	79.71
Immediate Release Layer of Losartan Potassium			
S.NO	Time (mins)	Amount of drug release (mg)	Cumulative Drug release (%)
1.	5	18.45±0.23	38.05
2.	10	25.38±0.54	52.38
3.	15	32.39±0.87	66.85
4.	20	35.61±0.75	73.50
5.	25	36.25±0.39	74.81
6.	30	37.60±0.81	77.59

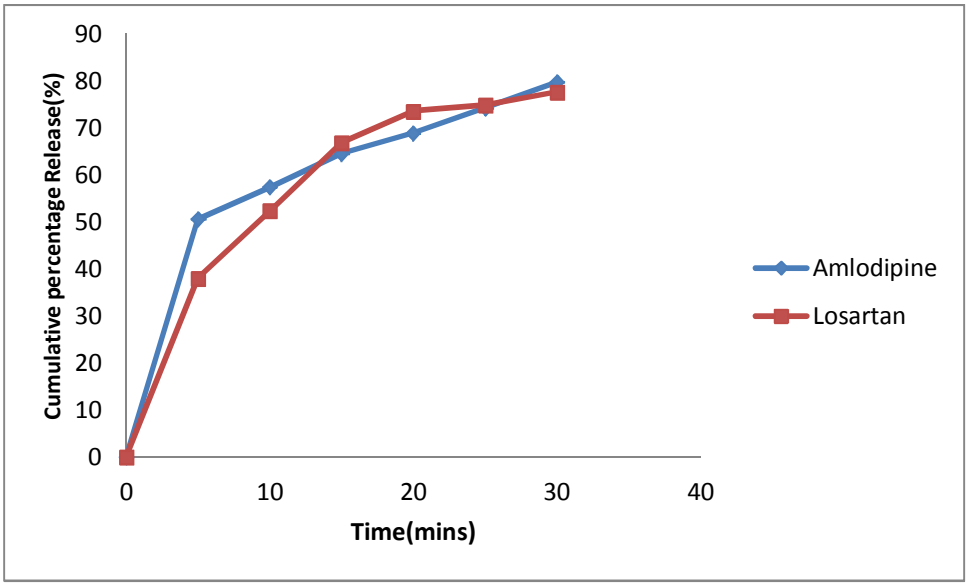


Figure 23: ***In vitro*** **Dissolution Profile of Formulation F-3**

Table 30 :*In vitro dissolution profile of Bilayer tablet* F-4

Immediate Release Layer of Amlodipine Besylate			
S.NO	Time (mins)	Amount of drug release (mg)	Cumulative Drug release (%)
1.	5	2.62±0.09	55.87
2.	10	3.01±0.16	64.12
3.	15	3.33±0.14	71.26
4.	20	3.60±0.11	77.10
5.	25	3.78±0.10	80.90
6.	30	3.83±0.25	82.23
Immediate Release Layer of Losartan Potassium			
S.NO	Time (mins)	Amount of drug release (mg)	Cumulative Drug release (%)
1.	5	22.12±0.56	45.67
2.	10	30.04±0.41	61.95
3.	15	35.78±0.67	73.82
4.	20	37.63±0.78	77.65
5.	25	38.77±0.39	80.03
6.	30	38.90±0.61	80.29

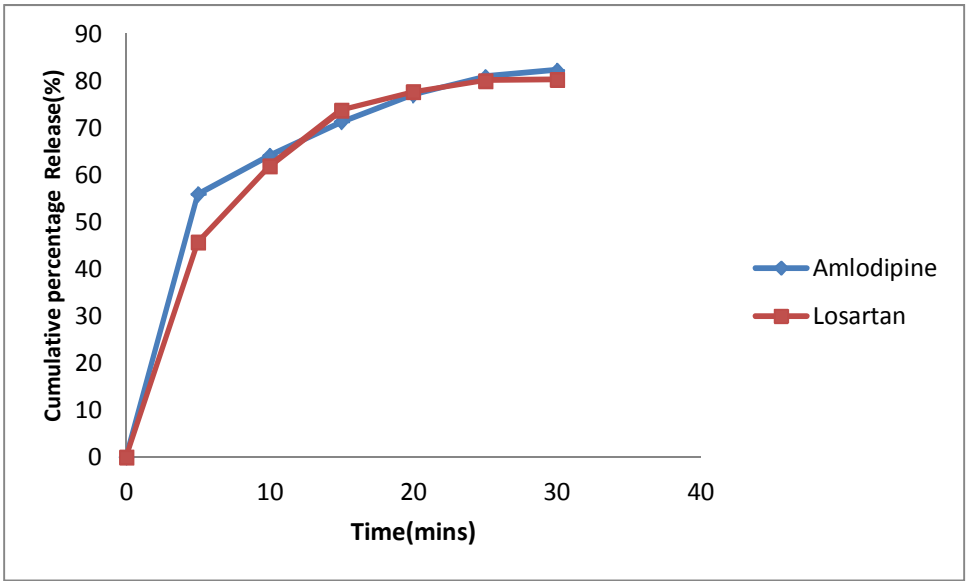


Figure 24: *In vitro* Dissolution Profile of Formulation F-4

Table 31: ***In vitro dissolution profile of Bilayer tablet*** **F-5**

Immediate Release Layer of Amlodipine Besylate			
S.NO	Time (mins)	Amount of drug release (mg)	Cumulative Drug release (%)
1.	5	3.39±0.10	72.13
2.	10	3.71±0.08	78.97
3.	15	3.85±0.12	82.13
4.	20	3.91±0.15	83.42
5.	25	3.93±0.11	83.91
6.	30	3.95±0.22	84.23
Immediate Release Layer of Losartan Potassium			
S.NO	Time (mins)	Amount of drug release (mg)	Cumulative Drug release (%)
1.	5	29.93±0.29	61.72
2.	10	34.98±0.12	72.17
3.	15	37.01±0.45	76.32
4.	20	39.52±0.26	81.56
5.	25	40.68±0.47	83.94
6.	30	41.46±0.19	85.56

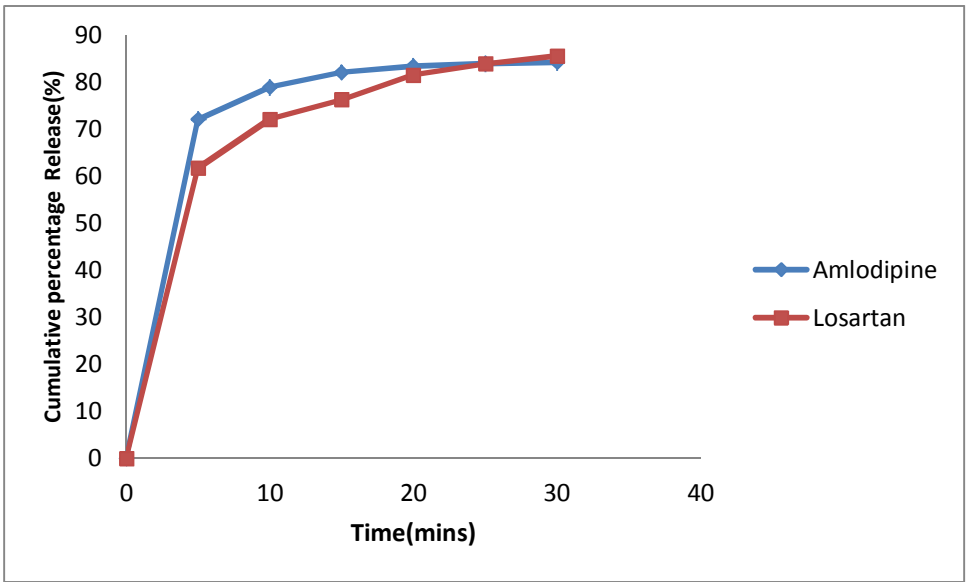


Figure 25: ***In vitro*** **Dissolution Profile of Formulation F-5**

***Table 32: In vitro dissolution profile of Bilayer tablet* F-6**

Immediate Release Layer of Amlodipine Besylate			
S.NO	Time (mins)	Amount of drug release (mg)	Cumulative Drug release (%)
1.	5	3.37±0.08	71.87
2.	10	3.63±0.12	77.46
3.	15	3.87±0.10	82.76
4.	20	3.90±0.18	83.15
5.	25	3.94±0.19	84.12
6.	30	3.97±0.17	84.88
Immediate Release Layer of Losartan Potassium			
S.NO	Time (mins)	Amount of drug release (mg)	Cumulative Drug release (%)
1.	5	33.53±0.49	69.14
2.	10	37.27±0.34	76.87
3.	15	39.52±0.70	81.53
4.	20	40.82±0.45	84.21
5.	25	42.13±0.34	86.92
6.	30	42.23±0.38	87.15

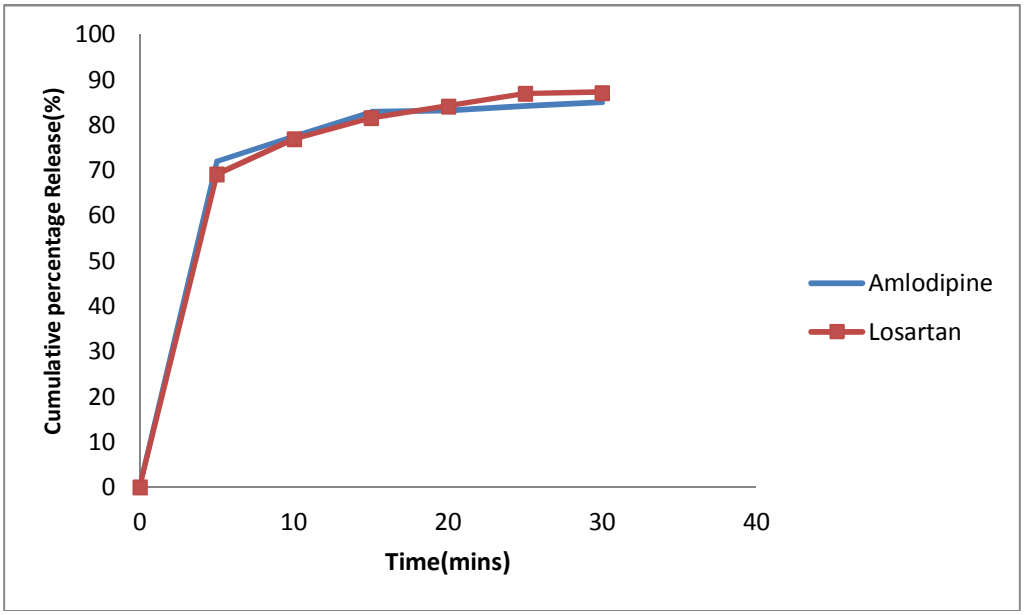


Figure 26: *In vitro* Dissolution Profile of Formulation F-6

Table 33: ***In vitro dissolution profile of Bilayer tablet*** **F-7**

Immediate Release Layer of Amlodipine Besylate			
S.NO	Time (mins)	Amount of drug release (mg)	Cumulative Drug release (%)
1.	5	3.31±0.05	70.53
2.	10	3.67±0.11	78.12
3.	15	3.81±0.09	81.23
4.	20	3.87±0.15	82.87
5.	25	3.93±0.18	84.25
6.	30	3.95±0.14	84.32
Immediate Release Layer of Losartan Potassium			
S.NO	Time (mins)	Amount of drug release (mg)	Cumulative Drug release (%)
1.	5	35.94±0.31	74.12
2.	10	38.14±0.44	78.70
3.	15	40.82±0.19	84.21
4.	20	41.98±0.54	86.78
5.	25	42.95±0.29	88.79
6.	30	43.17±0.28	89.09

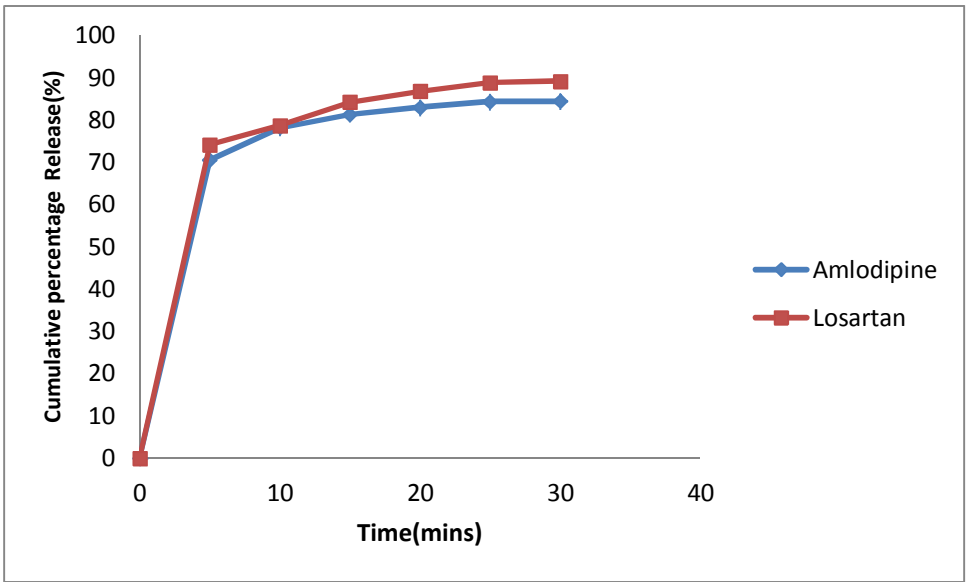


Figure 27: ***In vitro*** **Dissolution Profile of Formulation F- 7**

***Table 34 :In vitro dissolution profile of Bilayer tablet* F-8**

Immediate Release Layer of Amlodipine Besylate			
S.NO	Time (Mins)	Amount of Drug Release (mg)	Cumulative Drug Release (%)
1.	5	3.43±0.06	73.12
2.	10	3.72±0.08	79.54
3.	15	3.84±0.14	82.17
4.	20	3.90±0.12	83.21
5.	25	3.92±0.11	83.64
6.	30	3.93±0.15	84.02
Immediate Release Layer of Losartan Potassium			
S.NO	Time (Mins)	Amount of Drug Release (mg)	Cumulative Drug Release (%)
1.	5	37.66±0.55	77.67
2.	10	40.50±0.48	83.82
3.	15	41.22±0.37	85.05
4.	20	42.71±0.71	88.12
5.	25	43.55±0.68	89.85
6.	30	43.65±0.42	90.08

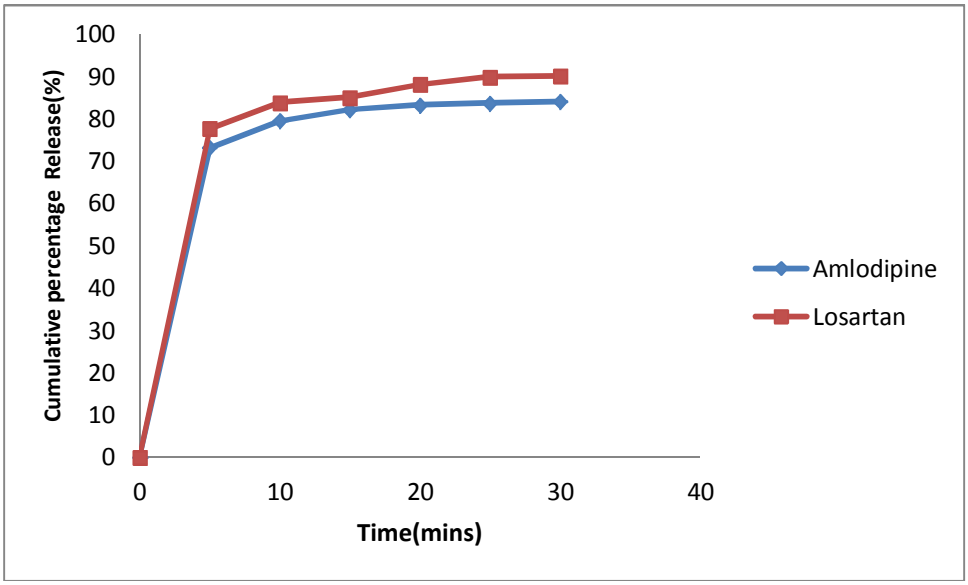


Figure 28: *In vitro* Dissolution Profile of Formulation F-8

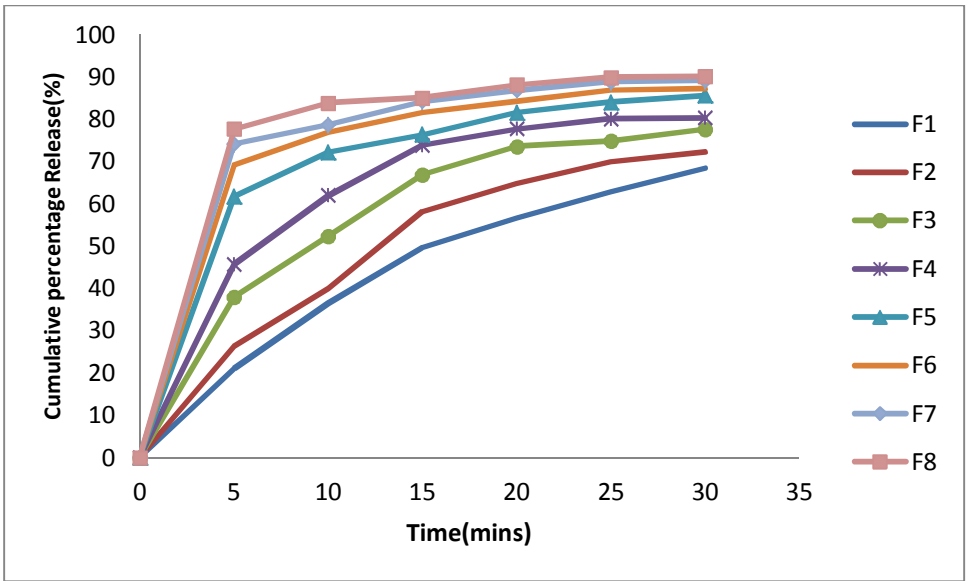


Figure 29 ***In vitro*** **Dissolution Profile of Losartan trials**

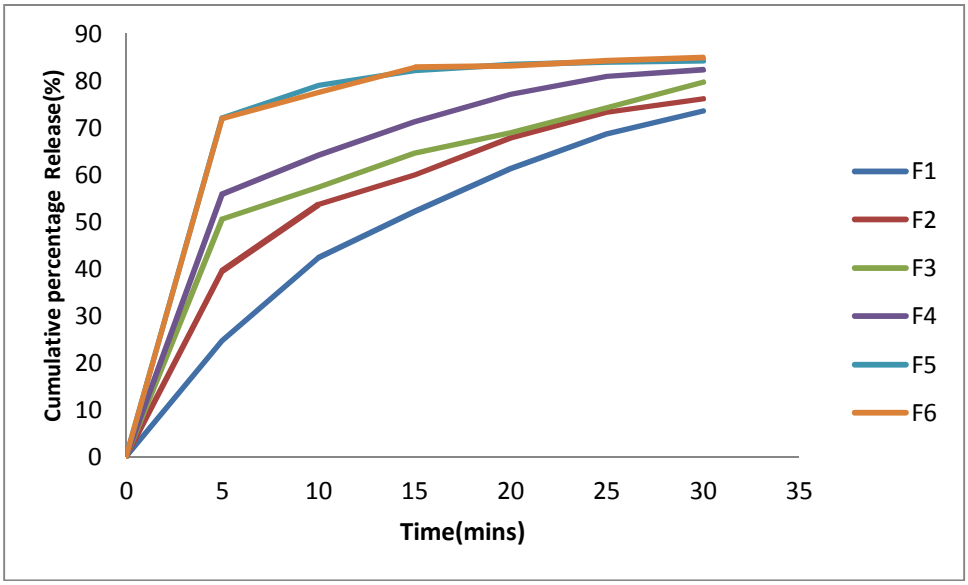


Figure 30: ***In vitro*** **Dissolution Profile of Amlodipine trials**

Table 35: *In vitro* dissolution profile of Market formulation

S.No	Time (mins)	Cumulative percentage drug release for Amlodipine (%)	Cumulative percentage drug release for Losartan (%)
1.	5	71.54	76.65
2.	10	77.36	84.12
3.	15	78.13	86.41
4.	20	78.79	89.98
5.	25	79.12	91.74
6.	30	79.95	92.56

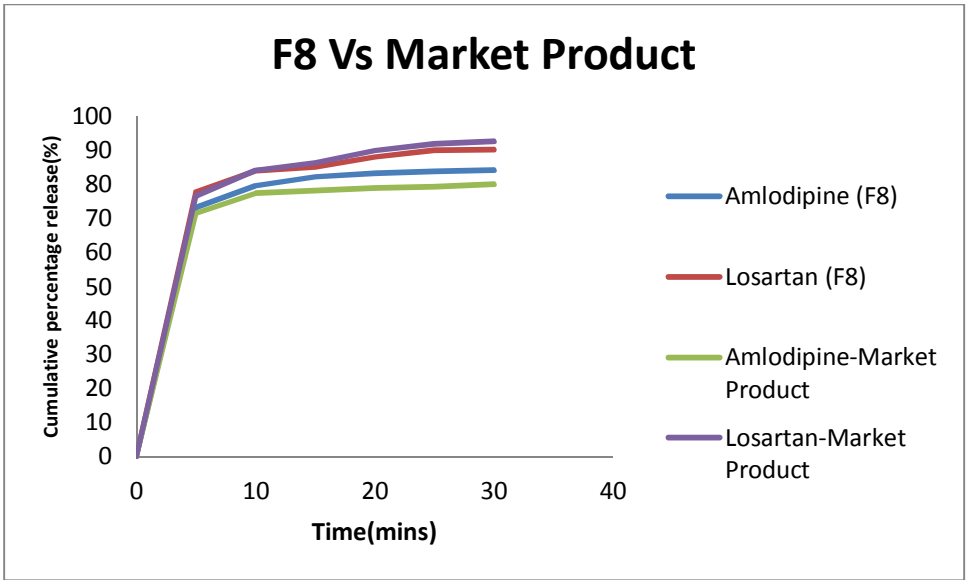


Figure 31: Comparison of Dissolution profiles of Optimized Formulation F8 and Marketed formulation

Model Chromatograms
Dissolution

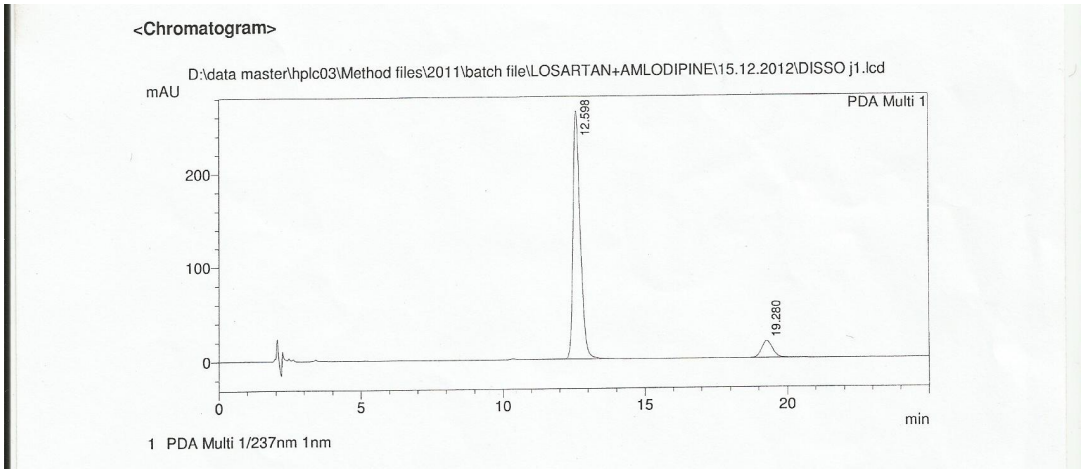


Figure 32: Dissolution sample

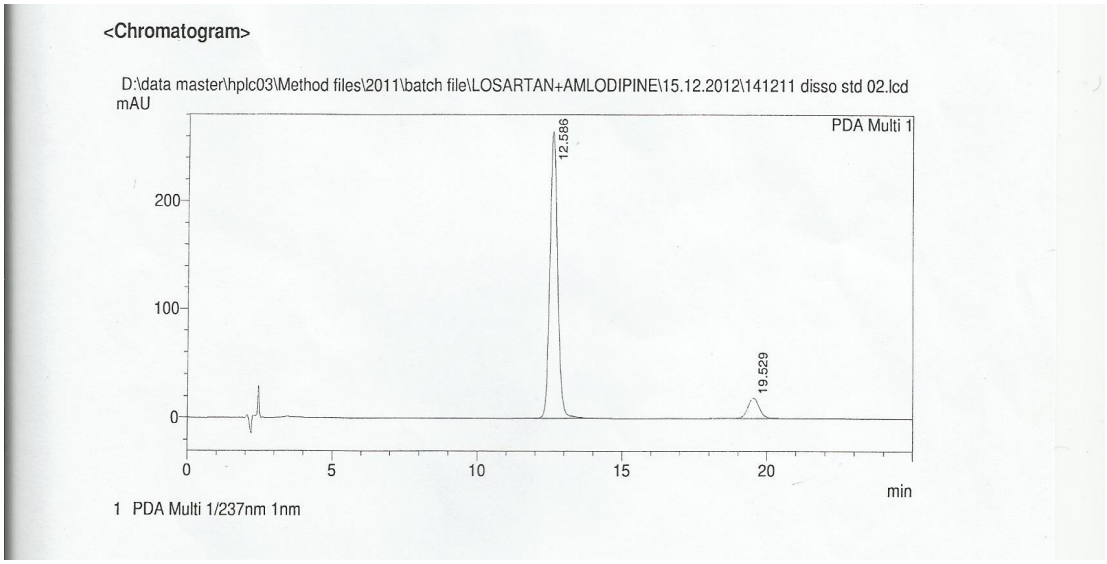


Figure 33: Dissolution standard

Table 36:Optimized Formulation Parameters- F8

S.NO	Test	Optimized Formulation (F8)
1.	Description	Yellow colour,circular,slightly,biconvex,plain,film Coated
2.	Average Weight(Mg)	363±4
3.	Identification Test (a) Amlodipine Besylate (b) Losartan Potassium	 (a) Complies (b) Complies
4.	Thickness(mm)	4.31±0.014
5.	Assay (a) Amlodipine Besylate (b) Losartan Potassium	(a)94.70% (b)96.87%
6.	Dissolution (a) Amlodipine Besylate (b) Losartan Potassium	(a)84.02% (b)90.08%

Table 37: Stability Studies

S.No	Parameters	Conditions				
		Initial	40°C& 75%RH	40°C& 75%RH	40°C& 75%RH	40°C& 75%RH
		0 Day	1 month	2 month	3 month	6 month
1	Average weight	363±5mg	363±5mg	363±5mg	363±5mg	363±5mg
2	Thickness(mm)	4.31±0.014	4.31±0.014	4.31±0.014	4.31±0.014	4.31±0.014
3	Disintegration time	6min45sec	7min17sec	7min23sec	7min20sec	7min 55 sec
4	Assay(%)	A-94.70	A-94.66	A-94.49	A-94.45	A-94.21
		L-96.87	L-96.81	L-96.74	L-96.72	L-96.50
5	Dissolution (30min)	A-84.02	A-83.98	A-83.89	A-83.86	A-83.53
		L-90.08	L-89.91	L-89.88	L-89.85	L-89.71

Discussion

8. Discussion

8.1. Calibration curves:

For Amlodipine besylate:

Calibration curve of Amlodipine besylate was prepared in 0.1N HCL at determined Wavelength 237nm.The calibration curve was linear between 2 to 20 µg/ml concentration ranges. The r^2 and slope were found to be 0.998 and 0.0323.

For Losartan Potassium:

Calibration curve of Losartan Potassium was developed in 6.8 pH buffer at above determined wavelength 235nm. The calibration curve was linear between 2 to 20 µg/ml concentration ranges. The r^2 and slope were found to be 0.9926 and 0.04485.

8.2. Preformulation studies:

It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, and compatibility studies.

Physicochemical Interaction of drug and Excipients:

The FTIR spectra of the drugs and its excipients are depicted in the figure 13-17.The spectra of standard Amlodipine Besylate and losartan potassium showed sharp charecteristics peaks at 3230.19cm^{-1},1687.41cm^{-1},2971.75cm^{-1}, 1116.92cm^{-1} and 3162.79cm^{-1},1665.69cm^{-1}, 3163.43cm^{-1} respectively.These peaks are also prominent in the spectra of the physical mixtures containing the drug and excipients in the formula of individual layers. This indicates there was no interaction between the drug and excipients.

8.3. Precompression studies:

8.3.1. Angle of repose

The angle of repose for the formulated blend was carried out and the results were shown in table No.22 and 23. It concludes all the formulations blend for amlodipine besylate was found to be in the range 26.30' to 29.40' and for losartan potassium it was found to be in the range of 26.20' to 32.50. Hence the entire formulations blend was found to be good, passable flow property.

8.3.2. Compressibility index

Compressibility index was carried out, it was found between 14.32% to 21.20% for Amlodipine besylate blend and 18.19% to 21.89% for losartan potassium blend indicating the powder blend has the required flow property for compression. The results were shown in table No.22 and 23

8.3.3. Hausner's ratio:

Hausner's ratio was calculated for the blend, it found between 1.16- 1.27 for amlodipine besylate and 1.09-1.26 for losartan potassium indicating Powder blend has the required flow property for compression. The results were shown in table No.22 and 23

8.5 Evaluation of Bilayer tablets

The measured hardness of tablets of each batch ranged between 6.4±0.57 to 8.9±0.69 kg/cm^2. This ensures good handling characteristics of all batches. The results were shown in Table No.24. The values of friability test were tabulated in Table No.24. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable. The percentage weight variations for all formulations were tabulated in Table No.26. All the formulated (F1 to F8) tablets passed weight variation test as the Percentage weight variation was within the pharmacopoeial limits of 7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values. The measured thickness of tablets of each batch ranged between 4.09±0.011to4.35±0.010mm for uncoated tablets and 4.21±0.011 to 4.46±0.012mm for coated tablets . The results were shown in Table No.24 and 25. The disintegration time of all the batches were found between 11 minutes to 6 minutes and results were shown in Table No 25. The percentage of drug content for F1 to F8 was found to 90.78% to 94.98% of Amlodipine besylate and 94.79% to 98.15% of Losartan Potassium and it complies with official specifications. The results were shown in table 25.

8.5.6. *In vitro* dissolution study

All the eight formulations of Amlodipine besylate and losartan potassium bilayer tablets, were subjected to *in vitro* release studies. Dissolution profiles of all formulations were compared by cumulative percentage drug release versus time. The percentage release of amlodipine besylate and losartan potassium at the end of 30 mins for F1 was found to be 73.62% and 68.40% which fails the official limits.The percentage release of amlodipine besylate and losartan potassium at the end of 30 mins for F2 was found to be 76.15% and 72.2% Respectively. The percentage release of amlodipine besylate and losartan potassium at the end of 30 mins for F3 was found to be 79.71% and 77.59% respectively.The percentage release of amlodipine besylate and losartan potassium at the end of 30 mins for F4 was found to be 79.71% and 77.59% respectively. The percentage release of amlodipine besylate and losartan potassium at the end of 30 mins for F5 was found to be 84.23% and 85.56% respectively. The percentage release of amlodipine besylate and losartan potassium at the end of 30 mins for F6 was found to be 84.88% and 87.15% respectively.The percentage release of amlodipine besylate and losartan potassium at the end of 30 mins for F7was found to be 84.32% and 89.09% respectively. The percentage release of amlodipine besylate and losartan potassium at the end of 30 mins for F8 was found to be 84.02% and 90.08% respectively. From dissolution results it was confirmed that formulation F8 was showing good dissolution profile in comparison to other batches and also according to pharmacopoeial limits. The optimized formulation(F8) was compared with that of marketed formulation and the results were found to be satisfactory.

The optimized formulation F8 containing 5 % w/w crospovidone for Losartan Potassium layer and 4% Sodium Starch Glycolate for Amlodipine layer shows least disintegration time and better dissolution properties compared to the other trail batches (F1- F7). The reason might be at the optimum concentration crospovidone rapidly exhibits high capillary action and pronounced hydration capacity and at optimum \ concentration of sodium starch glycolate disintegration occurs by rapid uptake of water followed by rapid and enormous swelling and hence F8 was choosen as the optimized formulation for the further stability studies.

8.6. Stability study

According to ICH guidelines, 6 months accelerated stability study at 40±2°c and 75±5% RH optimized formulation (F8) showed negligible change over time for parameters like appearance, drug content, dissolution, etc. No significant difference in the drug content between initial and formulations stored at 40±2°& 75±5% RH for 6 months.

Summary and Conclusion

SUMMARY

Amlodipine is a long-acting dihydropyridine calcium channel blocker. It is effective in the treatment of angina pectoris and hypertension, which has a biological half life of 30-
50 hours. Its dose is 2.5 to 10mg daily in divided doses. Losartan is a selective angiotensin II receptor blocking agent. It is useful mainly treatment of hypertension. It has a short biological half life of 2 hours and its dose is 40-80mg daily in divided doses.

In the present study an attempt was made to prepare Bilayer tablets of Amlodipine besylate (IR) and Losartan Potassium(IR) with excipients like MCC pH 102, SSG, aerosil & magnesium stearate for Amlodipine release layer and starch 1500, Crospovidone XL 10, aerosil & magnesium stearate for Losartan release layer.

Prepared bilayered tablets were evaluated for hardness, friability, weight variation, drug content uniformity, Drug-excipient interaction, in vitro drug release and stability studies. Among the various formulations prepared, Formulation F8 with SSG (4%) for amlodipine release and, (5%) of crospovidone XL 10 for losartan release Showed comparatively good release which complies with the dissolution requirements.

CONCLUSION

The present research was carried out to develop a Immediate Release Bilayer tablet of Amlodipine Besylate and Losartan Potassium. Combination of Amlodipine Besylate and Losartan Potassium are indicated for the successful treatment and relief of hypertension.

Prepared bilayer tablets were film coated in a conventional coating pan. Formulation characteristics such as content uniformity, hardness, friability were found to be satisfactory

In vitro dissolution studies of bilayer tablets were conducted for 30 minutes. Samples were analyzed by HPLC. The formulation (F-8) showed acceptable pharmacotechnical properties and complied with the internal specification for weight variation, thickness, hardness, friability, drug content and *in vitro* drug release. Reproducibility was checked by intra batch variability study and found no pronounced variation was observed.

Accelerated stability profile of bilayer tablets were found to be satisfactory. No sign of degradation was observed in HPLC analysis. Hence, it is finally concluded that, the Bilayer tablet technology can be successfully applied for Immediate-release of Amlodipine Besylate and Losartan Potassium.

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